FORMULATION AND IN VITRO EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ISRADIPINE

Dissertation submitted to

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In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

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Submitted by

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ISRADIPINE."** submitted by the student bearing **Reg. No:26103010** to "The Tamil Nadu Dr. M.G.R. Medical University", Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in **PHARMACEUTICS** was evaluated by us during the examination held on…….

Internal Examiner **External Examiner**

CERTIFIICATE

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DECLARATION

I hereby declare that the dissertation work entitled **"FORMULATION AND IN VITRO EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF ISRADIPINE"** is based on the original work carried out by me under the guidance of **Dr. V. VENU, M.Pharm, Ph.D**., for submission to The Tamil Nadu Dr. M.G.R Medical University, Chennai, in the partial fulfillment of the requirement for the award of **Degree of Master of Pharmacy** in Pharmaceutics. The work is original and has not been submitted in part or full for the award of any other Diploma or Degree of this or any other University. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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CONTENTS

CHAPTER	TITLE	PAGE NO.
1	**INTRODUCTION**	1
2	**LITERATURE REVIEW**	24
3	**AIM AND OBJECTIVE**	32
4	**PLAN OF WORK**	34
5	**DRUG AND EXCIPIENT PROFILE**	35
5.1	Drug profile	35
5.2	Excipient profile	39
6	**MATERIALS AND METHODOLOGY**	46
6.1	Materials	46
6.2	Methodology	48
6.2.1	Preformulation studies	48
6.2.2	Formulation of controlled release matrix tablet	54
6.2.3	Evaluation of controlled release matrix tablet	58
6.3	Kinetic studies	60
6.4	Stability studies	63
7	**RESULTS AND DISCUSSION**	65
8	**SUMMARY AND CONCLUSION**	87
9	**BIBLIOGRAPHY**	90

1. INTRODUCTION

1.1. ORAL DRUG DELIVERY

Oral drug delivery is the most widely utilized route of administration among all the routes of administration that has been explored for the systematic delivery of drug through different pharmaceutical dosage forms. The popularity, of oral drug delivery may be in partly attributed to its ease of administration as well as the traditional belief that by oral administration, the drug is well absorbed because of the food stuff that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form(solid, semisolid or liquid dosage forms), involves various extent of optimization of dosage form characteristics within the inherent consistent of gastro intestinal physiology.[1]

The oral route of drug administration is the most important method of drugs for systematic affects. It can be said that at least 90% of all drugs used to produce systemic effect by oral route of drugs that are administered orally, solid oral dosage forms represents the preferred loss of product because in this form one usual dose of the drug has been accurately placed.[2]

1.2. ORAL CONTROLLED RELEASE DOSAGE FORMS

Oral drug delivery system is the most popular route, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. There is a plethora of oral controlled release products in the market place. Over the past decades the treatment of illness has been accomplished by administering dosage forms, like tablets, capsules, pills, creams, ointments, liquid, aerosols, injectables and suppositories.

These conventional drug delivery systems are still the primary pharmaceutical products commonly seen today in the prescription and OTC drug market place. To achieve and maintain the drug concentration in the body with in the therapeutic range required for a medication, it is often necessary to take this type of drug-delivery system several times a day. This results in a see saw pattern drug level. [3]

Figure 1: Fluctuating drug levels and frequent dosing in case of IR products

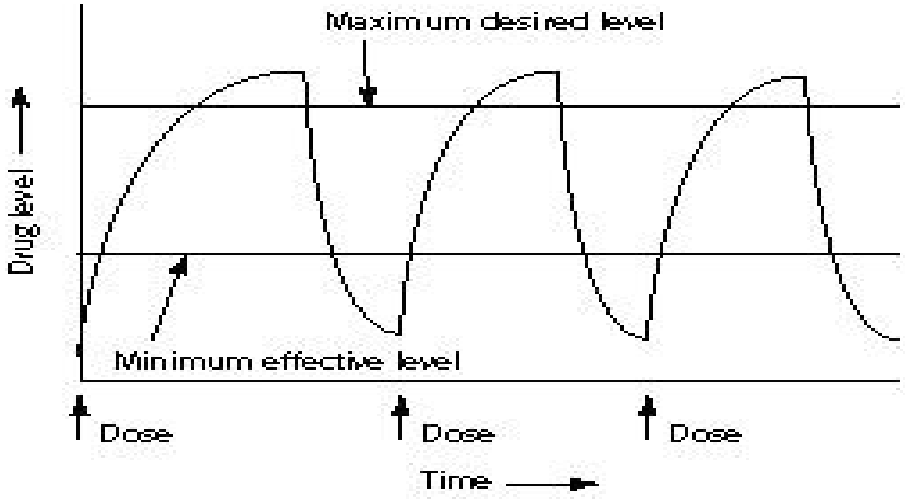
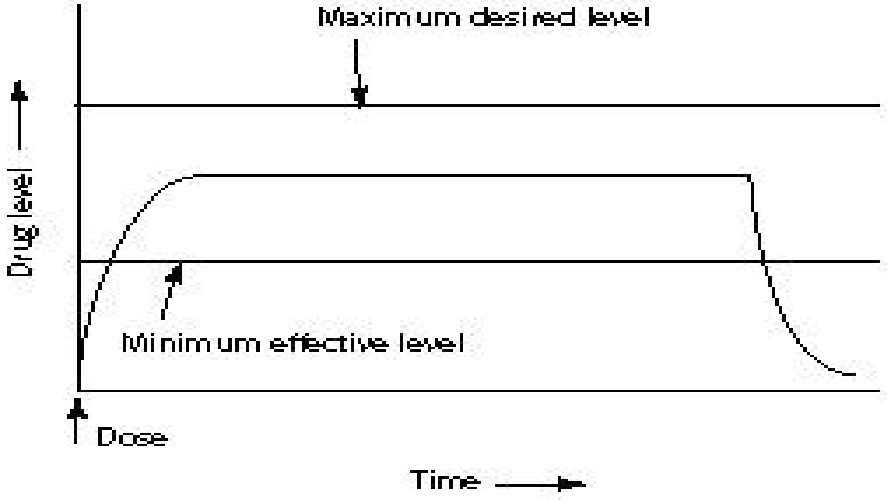


Figure 2: Drug blood level time curve for a controlled release product



A number of technical advancements have been recently made in developing new technologies for the rate of drug ,delivery sustaining the duration of the therapeutic action and /or targeting the delivery of drug to a tissue. These advancements have already led to the development of several novel drug drug delivery systems that could provide one/more of the following.[4]

1) Controlled administration of a therapeutic dose at a desirable delivery state.

2) Maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.

3) Maximization of efficacy-dose relationship.

4) Reduction of side effects.

5) Maximization of the needs for fragments dose intake and patient compliance.

1.3. ADVANTAGES AND DISVANTAGES OF ORAL CONTROLLED RELEASE DELIVERY SYSTEM

Development of oral controlled release dosage forms of a given drug involves optimization of the dosage form characteristics within the inherited constrains of the gastrointestinal physiology. Controlled release delivery systems have added advantages over immediate release dosage form.

Advantages:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- Reduction of dosing frequency by administering the drug once or twice a day.
- Drug administration can be more convenient due to reduction of gastrointestinal side effects.
- Less fluctuation of plasma drug level and leads to more uniform drug effect and lesser total dose.
- Maximization of efficiency-dose relationship.
- Improved patient compliance.
- Minimize or eliminate local side effects.

- Employ less total drug than that in combined conventional dosage forms.
- Minimize drug accumulation with chronic dosing.
- Reduction in health care costs.i.e, the average cost of treatment over an extended time period may be less with lesser frequency of dosing.

Disadvantages:

One the other hand, controlled release dosage forms have some disadvantages which include,

- Relatively poor in-vitro/in-vivo correlation.
- Increased variability among dosage units.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.
- Need for additional counseling of patients.

1.4 .CONTROLLED RELEASE FORMULATIONS

Table no.1: Type of controlled release system

TYPE OF SYSTEM	RATE CONTROLLING MECHANISM
Diffusion controlled • Reservoir system • Monolithic system **Water permeation controlled** • Osmotic system • Swelling system **Chemically controlled** • Monolithic system • Pendent system ion exchange resins **Regulated systems** • Magnetic, ultrasound • Chemical	Diffusion through a membrane Osmotic transport of water through a semi permeable membrane Water penetration into a glassy polymer Either pure polymer erosion (surface erosion)or a combination of erosion and diffusion(bulk erosion) Combination of hydrolysis of the pendent group and diffusion from the bulk polymer Exchange of acidic or basic drugs with ions present External application of magnetic field or ultrasound device Use of competitive desorption or enzyme substrate reactions. Rate control is built into the device.

I.TYPES OF CONTROLLED RELEASE TABLETS

1. Matrix type tablets

a) Hydrophobic and hydrophilic matrices.

b) Plastic matrices.

c) Ion exchanges resins.

d) Co-precipitates and solid dispersions.

2. Film-Coated tablets

a) Diffusion-controlled membranes.

b) Osmotic pumps.

c) Enteric coating tablets.

d) Floating tablets.

e) Swellable tablets.

f) Mucoadhesive tablets.

g) Complexation.

h) Cyclodextrins.

i) Pharmaceutical adhesives.

3. Multiple-unit tablets

II. CAPSULES

a) Hard capsules

b) Soft elastic capsules

c) Floating capsules

III. Micro granules/spheroids

IV. Beads

V. Pellets

VI. Emulsions

VII. Suspensions

VIII. Liposome's

IX. Micro particles

X. Nano particles

1.5. MATRIX SYSTEMS

Types of oral controlled release tablets

1) Matrix type/matrix systems.

2) Film coating tablets.

3) Multiple unit tablets

1.5.1. Matrix tablets:

These are the simplest and least expensive system for controlled drug delivery. Their processing is reproducible and is similar to that conventional system. The polymer or other carrier is homogeneously mixed with drug.

Drug release from the bulk of matrix involves two matrix mechanisms:

1) The erosion rate of the matrix determines the drug release state in matrices governed by erosion or dissolution

$$\left(\frac{dm}{dt}\right) = S\left(\frac{dx}{dt}\right) f(c) \qquad \textit{Eq.}\ (1)$$

Where:

$\left(\frac{dm}{dt}\right)$- Drug release rate.

S - Surface area

$\left(\frac{dx}{dt}\right)$- Matrix erosion rate

$f(c)$- Drug Concentration gradient

2) The diffusion through a barrier membrane describes drug release in insoluble coating via fick's second law of diffusion.

$$\left(\frac{dm}{dt}\right) = DSK\ \frac{(Cd-Cr)}{h} \qquad \textit{Eq.}\ (2)$$

Where:

D – Diffusion coefficient

S – Exposed surface area

K –Partition coefficient

$(Cd - Cr)$– Drug concentration gradient

1.5.2. Avantages of matrix system

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipment's. Secondly, development cost and time associated with the matrix system are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accomodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

1.5.3. Limitation of the matrix systems

As with any technology, matrix systems come with certain limitations. First matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

1.5.4. Types of matrix systems

The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

1.5.4 (a) Hydrophobic matrix system

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic. The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index.

.1.5.4 (b) Hydrophilic matrix system

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the

penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glassy-rubbery temperature (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix Boniferoni *et al*. (1995) showed a relationship between rheological behavior of HPMC gels and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to erosion. In turn, they affect drug release rate in the case of poorly soluble drugs.[6]

Swelling controlled release systems are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.

Drug release from swell able matrix tablets can be affected by glassy-rubbery transition of polymer (as a result of water penetration into the matrix where interaction among water, polymer and drug or fillers is considered as the primary factor for release control) and the various formulation variables, such as polymer

grade and type, drug to polymer ratios, drug solubility, drug and polymer particle sizes, compaction pressure and presence of additives or excipients in the final formulation.

1.6. DRUG RELEASE FROM MATRIX SYSTEMS

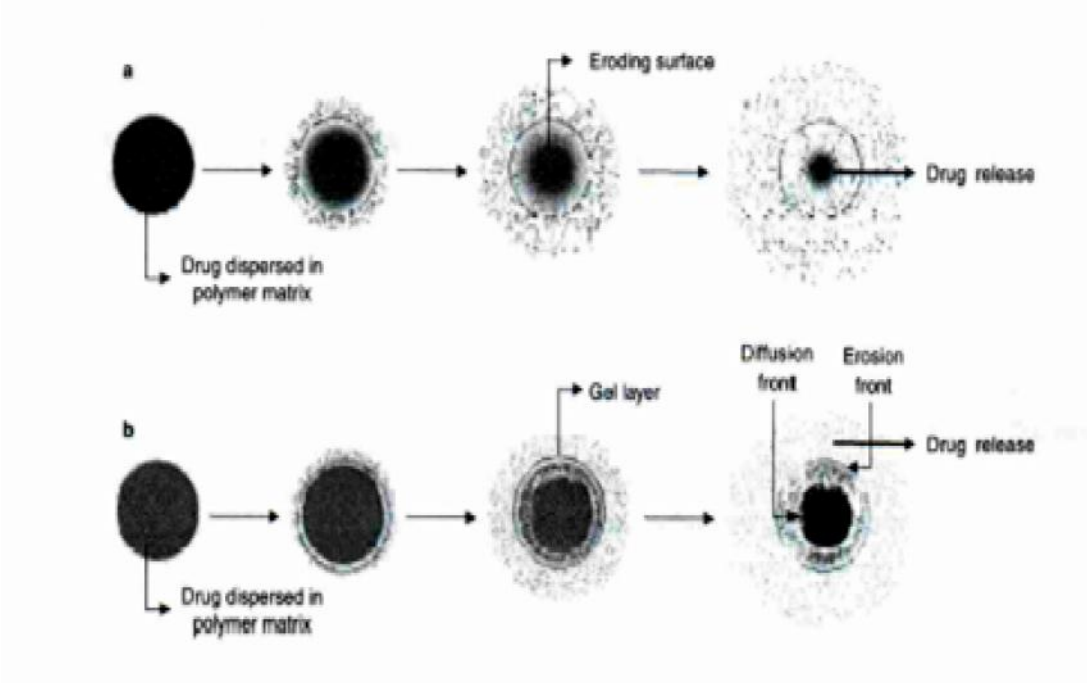
1.6.1. Mechanism of drug release from swelling controlled release systems

1.6.1 (a) Polymer swelling and drug release

The overall drug release mechamism from swelling controlled release systems based pharmaceutical devices strongly depends on the design (composition and geometry) of the particular delivery system. When a matrix comes in contact with an aqueous solution, wetting occurs first at the surface and then progresses by way of microscopic pore spaces into the matrix. The excipient in the matrix also absorb water, hydrates and swell to block up the existing pores, dissolves the content to create a more porous structure, gels to form a more viscous solution giving rise to positive pressure opposing liquid entry or causes disintegration of the matrix. Before a liquid can enter a matrix, there must be a driving force, which is derived from the pressure difference. The rate of liquid penetration into the matrix is determined by balance of this force promoting fluid entry towards the interior and the viscous force opposing it, which soon develops as soluble excipients in matrix dissolve or swell. The swelling of the matrix and consequent drug release by diffusion from the matrix and erosion of the matrix is shown in Figure 3a and 3b.

Figure 3(a) Drug release controlled by polymer erosion;

3(b) Drug release controlled by swelling and erosion.

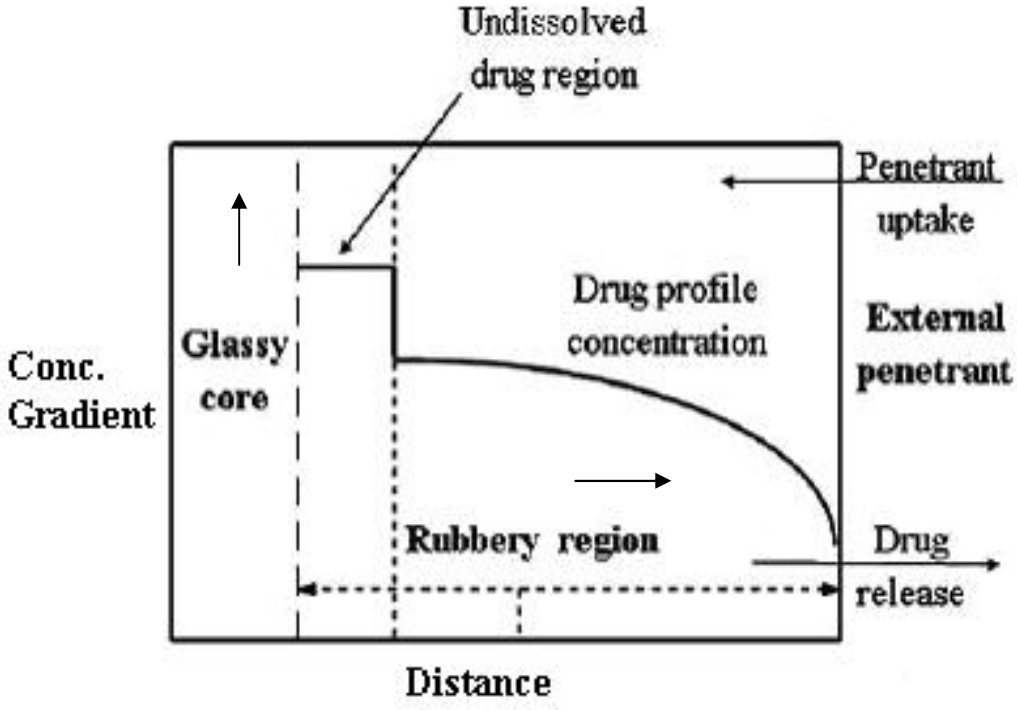


A hydrophilic matrix, controlled-release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling, and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away. The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer, present throughout the tablet, hydrates on the outer tablet surface to form a gel layer. Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion.[8]

A detailed description of the swelling, erosion and drug release process can be described as follows.

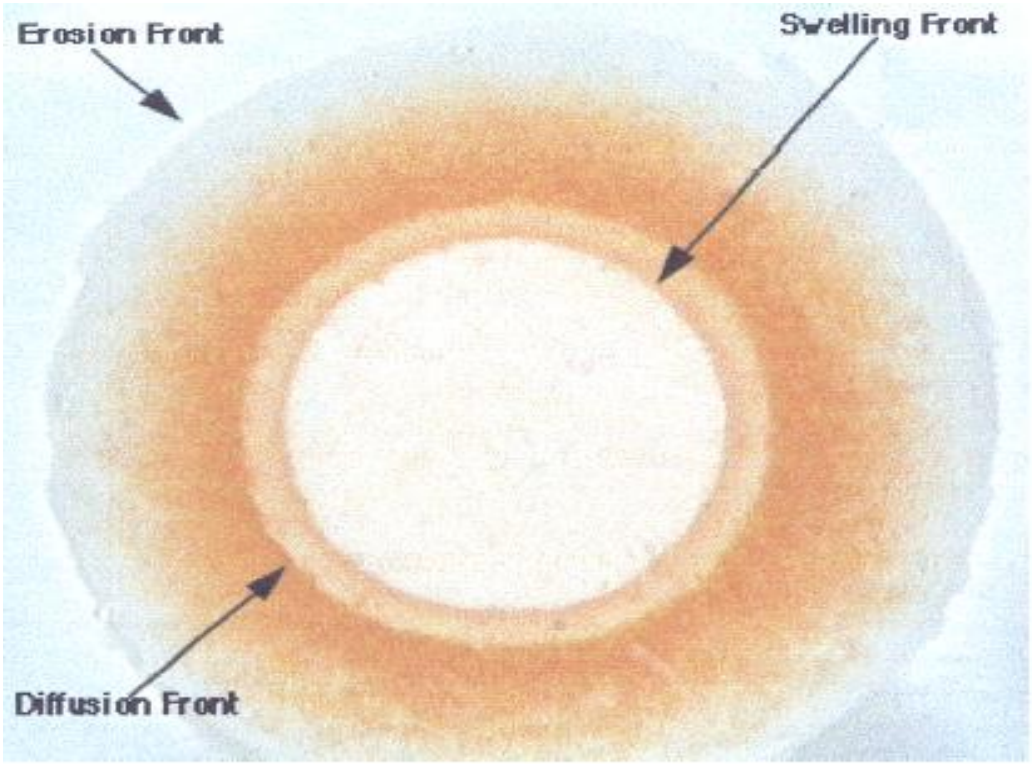
i). At the beginning of the process, steep water concentration gradients are formed at the polymer water interface resulting in water imbibitions into the matrix. In dry systems the diffusion coefficient is very low, whereas in highly swollen gels it is of the same order of magnitude as pure water. Water acts as a plasticizer and reduces the glass transition temperature (*Tg*) of the system. Once the *Tg* equals the temperature of the system, polymer chains undergo the transition from the glassy to the rubbery states shown in Figure 4. The glass transition temperature *Tg*, of a polymer is an important characteristic constant, in particular with respect to applications in the field of controlled drug delivery. Below the *Tg* the mobility of the macromolecules is very low[9]. The material is in its glassy state resulting in extremely small diffusion. In contrast, above the glass transition temperature the mobility of the polymer chains is markedly increased (rubbery state), leading to much higher mass transfer rates of water and drug. For instance Tg for HPMC is reported to be 154 to 184^{o}C.[10]

Figure 4: Drug concentration profile as a function of glass and rubbery regions[9].



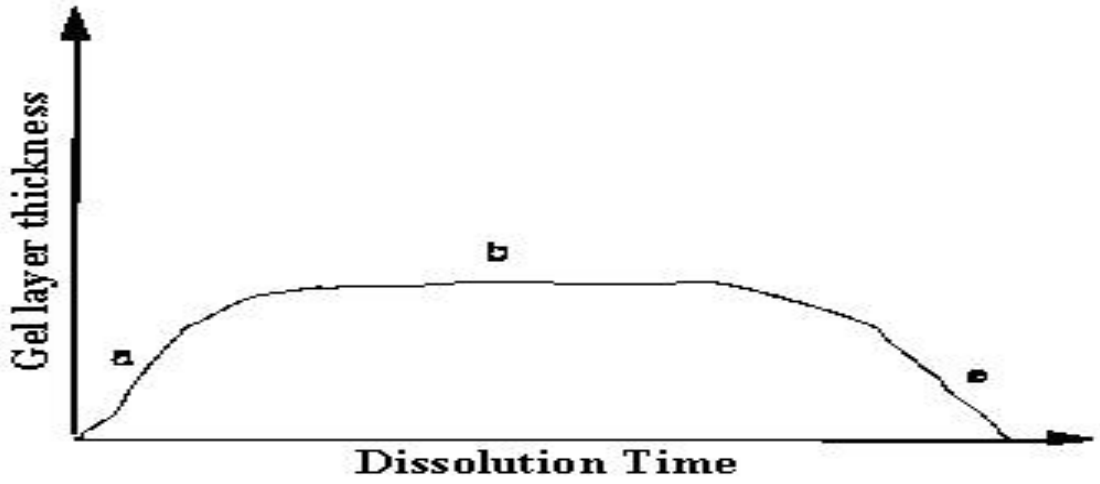
ii). The imbibitions of water and formation of rubbery region; which externally appears as polymer swelling results in dramatic changes of polymer and drug concentrations, and increasing dimensions of the system. The polymer chains unfold, and gradually become solvated, voids created as the polymer unfolds is occupied by water molecules. The apparent volume occupied by these expanded coils is referred to as the hydrodynamic volume.

Figure 5: Different front position observed during matrix swelling and erosion.



iii). Upon contact with water the drug dissolves and (due to concentration gradient) diffuses out of the device. Three fronts are observed as shown in Figure 5.[11] The Swelling front, identifying the boundary between the still glassy polymer and its rubbery gel state. The boundary between the still undissolved (solid) drug and the dissolved drug in the gel layer is indicated by diffusion front and erosion front identifies the boundary between matrix and dissolution medium. Gao *et al*. (1996) studied the swelling behavior of HPMC matrices using Adinazolam mesylate as the model drug, and concluded that swelling is anisotropic with preferential expansion in the axial direction; swelling is isotropic with respect to the gel layer thickness and composition in both axial and radial directions.

Figure 6: Gel layer thickness as a function of time.



iv). With increasing water content the diffusion coefficient of the drug increases substantially. It is to be noted that during drug delivery, as swelling and dissolution of the polymer compete, the gel layer thickness first increases due to swelling (Region a in Figure 6), then remains constant due to synchronization of swelling, drug diffusion, and dissolution (Region b) and finally decreases (Region c) as dissolution takes over.

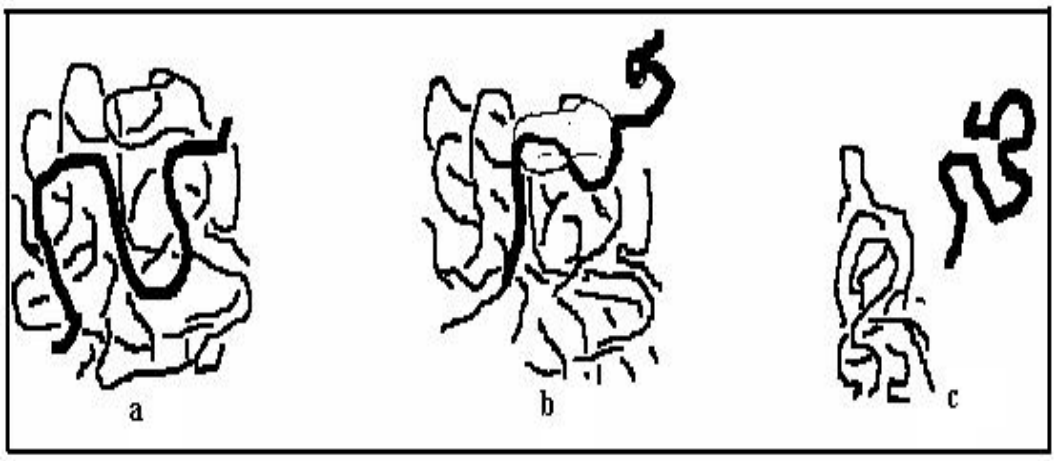
Thus finally the release of drug is complete as the matrix erodes. The drug release from a swelling matrix system thus can be summed up to be governed by drug diffusion through the matrix and polymer erosion. It is to be noted that in the case of poor water-solubility, dissolved and undissolved drug coexist within the polymer matrix. Undissolved drug is not available for diffusion. In the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon drug depletion. Depending on the chain length and degree of substitution of the HPMC type used, the polymer itself dissolves more or less rapidly (erosion of the polymer). In certain cases this phenomenon is negligible, for example if all the drug has already been released before polymer dissolution becomes important.

1.6.1. (b) Polymer erosion

Polymer chain dissolution from the matrix involves two distinguishable processes as depicted in Figure 8.

- The first step involves disentanglement of the individual molecules at matrix surface, which depend on rate of hydration. This occurs at a critical polymer concentration, defined as 'polymer disentanglement concentration. This polymer concentration depends on properties of the polymer and solvent.
- The second step involves the transport of these molecules from the surface across an aqueous diffusion layer, adjacent to the matrix, to the bulk solution[12]

Figure 7: A system showing polymer erosion, (a) initial polymer entanglement in the matrix, (b) reptating chain disentangling from the system and (c) finally disentangling from the system.



Here the disentanglement of the "bold" chain is considered. A test chain in an entangled system of chains is shown in (Figure 7a). When solvent penetrates into this system, the mobility of the test chain increases, and the chain begins to exhibit "reptation". Reptation causes the test chain to disentangle from the system (Figure 7b). The test chain completely disentangled from the original system is shown in (Figure 7c).

1.6.2. POLYMERS USED IN MATRIX SYSTEMS [13]

Tablet formation is one way of designing a controlled release form. Depending on the type of formulation or processing technique a number of parameters need to be controlled in matrix systems. Some examples illustrate such parameters used in polymer resin, plastic or wax based matrices. The chemical and physical effects of polymers on matrix have been reported. Chemical effects include water vs. solvent solubility, hydration gel formation and physical wettability, porosity, viscosity, cohesiveness, permeation and so on. Some examples follow:

Types of polymers used in matrix systems

1) Insoluble, inert
   a) Poly ethylene
   b) Poly vinyl chloride
   c) Methyl acryl ate – methacrylate copolymers
   d) Ethyl cellulose
2) Insoluble, erodible (Fatty compounds)
   a) Carnauba wax
   b) Stearyl alcohol
   c) Stearic acid
   d) Poly ethylene glycol
   e) Castor wax
   f) Poly ethylene glycol mono stearate
   g) Tri glycerides
3) Hydrophilic polymers
   a) Methyl cellulose
   b) Hydroxy ethyl cellulose
   c) Hydroxy propyl methyl cellulose
   d) Sodium carboxy methyl cellulose
   e) Sodium alginate
   f) Poly ethylene oxide
   g) Poly vinyl alcohol
   h) Galacto mannose

i) Carbopol
j) Hydroxy propyl cellulose
k) Guar gum
l) Alginic acid
m) Chitosan
n) Pectin

ETHYL CELLULOSE (EC):

- It is an insoluble, inert (plastic materials) type of polymer.
- Increasing the amount of EC resulted in decreased release rate.

HYDROXY PROPYL CELLULOSE (HPC):

- It is hydrophilic polymer. Mechanistic studies of HPC have shown gel formation, dissolution and diffusion to be important in controlling release.
- HPC > EC aqueous solutions 0.5% concentration have decreased viscosities in the order shown.
- Increasing the HPC concentration and viscosity decreases release rate of drugs. Possibly to both decreased porosity and cohesiveness of the matrix.

HYDROXY PROPYL METHYL CELLULOSE (HPMC):

- It is hydrophilic polymer. As amount of HPMC in the mixtures was increased dissolution of gel layer took place in addition to diffusion.
- Additives can be used to modify wettability of the pores and thus further increased and decreased the porosity[14].
- Release occurs initially from the surface particles via dissolution followed by pore formation in the area of the displaced surface drug particles with further solute diffusion.

HYDROXY ETHYL CELLULOSE

- Hydroxy ethyl cellulose is a non ionic, water-soluble polymer it in combination with Hydroxy propyl cellulose forms a good matrix system.

1.7. NEED FOR INVESTIGATION OF DRUG

Drug is a highly lipid soluble BCS class II drug used as an antihypertensive for the treatment of hypertension, angina pectoris. It is a yellow crystalline solid, insoluble in water (<10mg/L). The dose of the drug ranges from 10mg per day and its steady state half life is relatively short($1^{1/2}$-2hr).The bioavailability is very limited (15-24%) due to the hepatic first pass effect. While extended release of drug were originally developed to reduce or eliminate unwanted effects such as gastrointestinal disturbances, nausea, and vomiting; the short half life of the drug also indicates the need for modified release dosage form. Modified release solid oral dosage forms offer the advantages of improved patient compliance and decreased side effects. Majority of oral sustained and controlled release drug delivery systems are based on either gel forming matrix or coated formulations, or the combination thereof. Matrix tablet systems are most popular due to ease in scale-up. The drug is currently available in market as immediate release tablet and as an extended release capsule. At present the extended release tablets available in the market uses osmotic pressure to deliver the drug at a controlled rate over approximately 24 hours. The present research endeavor was directed towards the development of matrix tablets to be taken once daily reducing the price of drug and make the drug more affordable to the patients.

The value of hydrophilic, polymer based matrix system as carriers for controlled drug delivery is well recognized and increasingly demonstrated by the numerous patents, research papers, and U.S.FDA approved matrix based products. In particular, water soluble cellulose ethers (e.g., HPMC, HPC, HEC, EC), PEO, polyvinyl alcohols, carbopol, and polysaccharides such as xanthan gum; chitosan, alginic acid, pectin, and guar gum have been extensively used.

1.8. HYPERTENSION

Hypertension is a chronicmedicalcondition in which the blood pressure is elevated. It is also referred to as high blood pressure or shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.

Hypertension can be classified as either essential (primary) or secondary. Essential or primary hypertension means that no medical cause can be found to explain the raised blood pressure and represents about 90-95% of hypertension cases. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma)

Causes of Hypertension

1.8.1. Essential hypertension[15]:

Essential hypertension is the most prevalent hypertension type, affecting 90-95% of hypertensive patients Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, stress, visceral obesity, potassium deficiency (hypokalemia) obesity (more than 85% of cases occur in those with a body mass index greater than 25), salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency. Risk also increases with aging, some inherited genetic mutations and family history. An elevation of renin, an enzyme secreted by the kidney, is another risk factor, as is sympathetic nervous system over activity. Insulin resistance which is a component of syndrome X, or the metabolic syndrome is also thought to contribute to

hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

1.8.2. Secondary hypertension:

Secondary hypertension by definition results from an identifiable cause. This type is important to recognize since it's treated differently than essential type by treating the underlying cause. Many secondary causes can cause hypertension; some are common and well recognized secondary causes such as Cushing's syndrome, which is a condition where both adrenal glands can overproduce the hormone cortisol. Hypertension results from the interplay of several pathophysiological mechanisms regulating plasma volume, peripheral vascular resistance and cardiac output, all of which may be increased. More than 80% of patients with Cushing's syndrome have hypertension.] Another important cause is the congenital abnormality coarctation of the aorta

1.8.3. Mechanism of hypertension:

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased.

Three theoeies have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as is Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
- An overactive Renin-angiotensin system leads to vasoconstriction and retention and symptoms are especially important of sodium and water. The increase in blood volume leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses.

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Recently, work related to the association between essential hypertension and sustained endothelial damage has gained popularity among hypertension scientists. It remains unclear however whether endothelial changes precede the development of hypertension or whether such changes are mainly due to long standing elevated Blood Pressure.

1.8.4 Symptoms of hypertension:

Mild to moderate essential hypertension is usually asymptomatic. Accelerated hypertension is associated with headache, somnolence, confusion, visual disturbances, and nausea and vomiting (hypertensive encephalopathy). Some signs and symptoms are especially important in infants and neonates such as failure to thrive, seizure, irritability or lethargy, and respiratory distress In children, hypertension may cause headache, fatigue, blurred vision, epistaxis, and bell palsy.

Some signs and symptoms are especially important in suggesting a secondary medical cause of chronic hypertension, such as centripetal obesity, "buffalo hump," and/or wide purple abdominal striae and maybe a recent onset of diabetes suggest glucocorticoid excess either due to Cushing's syndrome or other causes..

Treatment of hypertension:

There are several types of antihypertensive agent;s

1. Adreno receptor blocking agents.

2. Diuretics.

3. Vasodilators.

A**) Calcium Channel Blockers**,

B) Directly Acting Vasodilators.

4. ACE inhibitors.

5. 5-HT antagonist.

1.8.5 Mechanism of action Calcium channel blockers: [16]

Calcium channel blockers work by blocking voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. This decreases intracellular calcium leading to a reduction in muscle contraction. In the heart, a decrease in calcium available for each beat results in a decrease in cardiac contractility. In blood vessels, a decrease in calcium results in less contraction of the vascular smooth muscle and therefore an increase in arterial diameter (CCB's do not work on venous smooth muscle), a phenomenon called vasodilation. Vasodilation decreases total peripheral resistance, while a decrease in cardiac contractility decreases cardiac output. Since blood pressure is determined by cardiac output and peripheral resistance, blood pressure drops.

With a relatively low blood pressure, the after load on the heart decreases; this decreases the amount of oxygen required by the heart. This can help ameliorate symptoms of ischemic heart disease such as angina pectoris.

Unlike β-blockers, calcium channel blockers do not decrease the responsiveness of the heart to input from the sympathetic nervous system. Since moment-to-moment blood pressure regulation is carried out by the sympathetic nervous system (via the baroreceptor reflex), calcium channel blockers allow blood pressure to be maintained more effectively than do β-blockers.

However, because calcium channel blockers result in a decrease in blood pressure, the baroreceptor reflex often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility. A β-blocker may be combined with a dihydropyridine calcium channel blocker to minimize these effects.

Ionic calcium is antagonized by magnesium ions in the nervous system. Because of this, dietary supplements of magnesium oxide and other magnesium preparations may increase or enhance the effects of calcium channel blockade.

LITERATURE REVIEW

1. Harekrishna Roy., (2010) ***et.al*** **.**[44] studied the design and in vitro evaluation of sustained release matrix tablets of complexed nicardipine hydrochloride by employing hydrophilic and hydrophilic polymers. Due to poor water solubility of the drug its bioavailability is dissolution rate limited. The purpose of the study was to increase the solubility of Nicardipine by cyclodextrin inclusion complex technique. Kneading method was employed for preparation of inclusion complexes. Among different complexes, a complex with 1:1 molar ratio of drug and β-CD showed the highest dissolution rate. Matrix tablets were prepared by direct compression technique using different concentration of polymers and selected complex. The study has demonstrated that combination of hydrophobic and hydrophilic polymers effectively sustained the drug release for prolonged period of time and a minimum of 28 % sodium alginate is required to retard the release of nicardipine from matrix tablet for the period of 12 hours.

2. Antesh K Jha., (2009) ***et.al*** [45] formulated and evaluated sustained release matrix tablets of Metoprolol succinate using hydrophilic polymers. The drug belongs to the category of β_1-selective adrenergic receptor blocking agent. The tablets were prepared by wet granulation method. Ethanolic solutions of ethylcellulose (EC) and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC) and guar gum. The results of dissolution studies indicated that formulation F1 (drug-to-HPMC, 1:4; ethanol as granulating agent) could extend the drug release up to 12 hours. In the further formulation development process, F5 (drug-to-HPMC, 1:4; EC 4% w/v as granulating agent), which is the most successful formulation of the study, exhibited satisfactory drug release. All the formulations exhibited diffusion- dominated drug release.

3. Dr.Ritesh Patel., (2009) ***et.al*** [46] studied the optimization of propranolol hydrochloride controlled release matrix tablet using factorial design. Direct compression technique was involved. HPMC K15M and Carbopol 934P were used in formulating the matrix tablets. A 32 full factorial design were applied for systemic studies. The blending ratio of HPMC K15M and Carbopol 934P (X1) and polymer

concentrations (X2) were the independent variables. The times required for 50% (t50) and 80% (t80) drug release were selected as dependent variables. The results indicated that the values of t50, t80, f2 and MDT are strongly dependent on the independent variables. in vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile. The results indicated that batch F7 showed the highest value among all the batches, and it also shows similarity in t50 and t80 values. The f2 value (74) of batch F7 indicates less than 5% difference in in vitro drug release profile with theoretical release profile.

4. SH Lakade., (2008) ***et.al*** [47] formulated and evaluated sustained release matrix tablet of anti-anginal drug, and studied the influence of combination of hydrophobic and hydrophilic matrix former. A hydrophobic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to a period of 24 hours in predetermined rate was developed. The formulation of Nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablets were also characterized by physical and chemical parameters. The in vitro release rate profile should be higher concentration in case of F2. The combination of hydrophilic and hydrophobic combination showed less result than use of alone. The in vitro release data was well fit to Peppas and Hixon crowel release kinetics.

5. Rupali Kale., (2010) ***et.al;*** [48] developed matrix diffusion controlled drug delivery system of pentoxifylline. HPMC formulations showed very high dissolution rate releasing 70% of drug within two hours but its combination formulation with Eudragit showed low dissolution rate of 0.14 $hour^{-1}$. Sodium alginate used did not show controlled drug release pattern. Eudragit and Guar gum formulations showed low dissolution rates indicating controlled release pattern of drug but their combination formulation showed high dissolution rate of 0.73 $hour^{-1}$.

6. Anroop B. Nair., ***et.al.***[49] formulated controlled release matrix uncoated tablets of Enalapril Maleate using HPMC alone. Direct compression techniques was used to prepare the tablets, and were evaluated for physical properties, drug content, in vitro release and drug release kinetics as well. All the formulations demonstrated good physical integrity and the drug content were in the official limits. The formulations with HPMC K 100 (25mg/tablet) and K4M (15mg/tablet) have been found to release the required amount of drug (2.97mg/h) throughout the study period (14h). The calculated regression coefficients showed higher r^2 value with Higuchi model and zero order kinetics. Given the excellent release profile, the study concluded that HPMC in different grades with low concentration alone can control the enalapril maleate release over a period of 14hours.

7. Hilde Celis, Jan Staessen, Robert Fagard, Lutgarde Thijis, and Antoon Amery., ***et al.***[50] studied effect of modified release 5 mg once daily isradipine on twelve patient with essential hypertension in a double blind cross over study to investigate the blood pressure BP-lowering activity, the results shows isradipine modified release 5 mg influenced the 24 hr BP profile in a different way when administered in the morning or in the evening as compared to placebo.

8. Saleh A. Al-Suwayeh., ***et al.***[51] studied transdermal delivery of isradipine through excised rabbit skin for the effect of vehicle and drug concentration, the vehicles namely PEG, ethanol and isradipine . Highest amount of isradipine over 24 hr period penetrated was achieved in presence of Ethanol.

9. Madhusmruti Khandai, Santanu Chakraborty, Anuradha Sharma, Debashisha Panda, Nazia Khanam, Santosh Kumar Panda., ***et al.***[52] studied on the development of Propranolol hydrochloride matrix tablets and Investigation on effects of combination of hydrophilic and Hydrophobic matrix formers like HPMC and EC and on its in-vitro release, and observed that 10% of each the polymer in combination was able to produce desire formulation which release more than 90% drug in 12 hours.

10. Juan G. Puig: Luis M. Ruilope; Rafael Ortega., *et al.*[53] studied the efficacy of antihypertensive treatment like benazepril in Type II Diabetes Mellitus to confirm the diagnosis of hypertension and assess the response to antihypertensive therapy. Antihypertensive drug efficacy was assessed by casual (trough) and 24-hour ambulatory blood pressure monitoring. Diabetic patients were classified as no confirmed hypertensive if the mean 24-hour ambulatory diastolic pressure was below 85 mm Hg. Antihypertensive treatment significantly decreased both systolic and diastolic pressures when determined by either casual measurement (from a mean of 162.7/98.0 to 153.9/89.2 mm Hg; $P<.001$) or ambulatory monitoring (from a mean of 143.1/84.4 to 137.0/81.5 mm Hg; $P<.05$).

11. Vaisse. B., Herpin D, Asmar R, Battistella P, Zannad F, Boutelant S, Lyon A, Co Denis J. Honore., *et al.*[54] Studies on the evaluation of the antihypertensive effect of drugs according to the initial ambulatory blood pressure (BP) level. In double-blind design, either bisoprolol (10 mg q.d.) or lisinopril (20 mg q.d.) for 8 weeks. BP monitoring showed that the antihypertensive effect depended on the baseline mean 24-h value; -15/-12 mm Hg for bisoprolol and -18/-13 mm Hg for lisinopril in the High group; -7/-6 mm Hg for bisoprolol and -6/-6 mm Hg for lisinopril in the Low group. This study shows that the antihypertensive effect depended on initial ambulatory BP values, with a lower BP decrease in the Low group.

12. Panna Thapa, Manish Ghimire, Alex B. Mullen and Howard N.E Stevens., *et al.* [55]studied on controlled release drug delivery system to investigate the influence of different diluents, in the release of poorly water soluble drug ibuprofen. Matrix tablet prepared by wet granulation method at different polymer concentration using lactose, DCP, MCC and starch. The integrity of the tablets and drug release were found to be primarily governed by the properties of diluents at low polymer concentration.

13. Bhanja Satyabrata, Ellaiah P, Mohanty Chandan, K.V.R Murthy ,Panigrahi Bibhutibhusan, Padhy Sudhir Kumar., *et al.*[56] studied on mucoadhesive buccal tablet containing antihypertensive drug i.e. Perindopril to avoid the first pass metabolism and to improve its bioavailability. The tablets were prepared by Prepared by Sintering Technique containing polymer Polyethylene oxide and carnauba wax.

The sintering times and the sintering temperature markedly affected the drug release properties of Perindopril buccal tablets; the release rate of Perindopril from buccal tablets was inversely related to the time of sintering and the sintering temperature. This is may be due to increase in extent and firmness of sintering which compacts the mass further, so that the drug release is affected. The best *in-vitro* drug release profile was achieved with the formulation F4 A (sintered at 600c for 1.5 hr.) which contain the drug, polyethylene oxide and carnauba wax in the ratio of 1:15:10.The surface pH, bioadhesive strength and swelling index of formulation F4 A was found to be 6.27, 34.8 gm and 179.31 (after 12 hr). The tablets (formulation F4 A) containing 4 mg of Perindopril exhibited 8 hrs sustained drug release (98 %) with desired therapeutic concentration.

14. Rajesh. N, Siddaramaiah and D.V. Gowda., *et al.*[57] studied on the controlled release behavior of diltiazem hydrochloride from the Pellets of chitosan and microcrystalline cellulose to minimize the unwanted toxic effects of Diltiazem Hydrochloride by kinetic control of drug release. 12 ml of deminerlized water was used as binding agent volume of binding agent increases, irregularly shaped pellets were produced. As the volume of the binding agent was less than 12 ml, requires more pressure for compaction and difficult to separate as an individual pellets. The percent of wetting solution and volume of binding agent has also an effect on the sphericity of the pellets, confirmed by SEM photographs. Result showed that lowered drug release was noticed for the systems containing higher content of MCC. Because swollen MCC particles retards the penetration of dissolution media into pellets and thus limiting the release of drug from pellets.

15. S. M. Al-Ghannam A. M. Al-Olyan., *et al.*[58] Studied on spectrophotometric determination of 1, 4-dihydropyridine compounds, nicardipine and isradipine. The method is based on the reduction of nicardipine and isradipine with zinc powder and calcium chloride followed by further reduction with sodium pentacyanoaminoferrate (II) to give violet and red products having the absorbance maximum at 546 and 539 nm with nicardipine and isradipine, respectively. Beer's law was obeyed over the concentration range 8.0–180 µg/ml with the detection limit of 1.67 µg/ml for nicardipine and 8.0–110 µg/ml with the detection limit of 1.748 µg/ml for isradipine.

The study shows high sensitivity (detection limit = 1.67 for Nicardipine and 1.74 µg/ml for Isradipine).

16. A Smith, J McPherson, M Taylor, A Mason, S Carney and A Gillies (1997) *et al.*[59] did a comparative study Atenolol and Isradipine. A 39%reduction of hypertension was seen with isradipine while 34% reduction with the other. Pro-haemorrhagic effects of Isradipine were minor when compared to Atenolol.

17. T Fujiwara, Y Ii, J Hatsuzawa, H Murase, T Watanabe, M Murakami, N Kimura, J Buch, T Tsuchihashi and T Saruta (2009) *et al.*[60] Worked on two strengths of Amlodipine, an antihypertensive drug. Phase III double-blind parallel-group controlled study was conducted to examine the superiority of Amlodipine 10 mg once daily to Amlodipine 5 mg once daily in 305 Japanese outpatients with essential hypertension .In conclusion, Amlodipine 10 mg once daily was found to be superior to Amlodipine 5 mg once daily, safe, well tolerated and useful for the relevant subjects.

18. Lacourcière Y, Poirier L, Dion D, Provencher P *et al.*[61] The antihypertensive efficacy of sustained-release Isradipine administered once daily compared to the immediate-release formulation administered twice daily was assessed by ambulatory blood pressure (BP) monitoring in a double-blind randomized crossover study in 76 mild-to-moderate hypertensive patients. Data suggest that sustained-release Isradipine has a sustained antihypertensive effect throughout 24 hours comparable to that of Isradipine given twice daily and may improve compliance with long-term treatment. In addition, the results confirm the usefulness of ambulatory BP monitoring in determining truly hypertensive patients likely to respond to drug administration.

19. Bankole A. Johnson, Martin A. Javor, Yui-Wing Francis Lam, Lynda T. Wells, *et al.* [62] The authors sought to determine whether sustained-release (SR) Isradipine provided comparable systemic availability to that of immediate-release (IR) Isradipine in non-treatment-seeking, cocaine-dependent individuals .The relative bioavailability of the SR formulation was 55.5% of that of the IR formulation. The more favorable cardiovascular profile of SR Isradipine would, however, make it more

appropriate as an investigational medication for the treatment of stimulant dependence and related neurovascular disorders.

20. Raslan & Maswadeh (2006) *et al.*[63] have studied the effect of HPMC (hydrophilic) and glyceryl behenate (hydrophobic) polymers on controlled release of anhydrous Theophylline matrix tablets and studied *in vitro* release characteristics and kinetics of prepared formulations for explaining the release pattern from matrix tablets.

21. Selim., (2003) *et al.*[64] Have done the comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. They revealed that the drug release from plastic and hydrophobic matrix was less than hydrophilic polymer. Again, the release pattern of drug from hydrophilic matrices was closer to zero-order kinetics than that from other classes of matrices.

22. Nair.,(2007) *et al.*[65] Have made an attempt to formulate a controlled-release matrix tablet formulation for Alfuzosin hydrochloride by using low viscous hydroxyl propyl methylcellulose (HPMC K-100 and HPMC 15cps) and its comparison with marketed product. Drug release from the matrix tablets was carried out for 12 hr and showed that the release rate was not highly significant with different ratios of HPMC K-100 and HPMC15cps. They concluded that the use of low viscous hydrophilic polymer of different grades (HPMC K-100 and HPMC 15cps) can control the Alfuzosin release for a period of 12 hr and were comparable to the marketed product.

23. Gurvinder Singh Rekhi, Ranjani V. Nellore, Ajaz S. Hussain, Lloyd G. Tillman, Henry J. Malinowski and Larry L. Augsburg., *et al* [66] worked on Identification of critical formulation and processing variables for Metoprolol Tartrate extended-release (ER) matrix tablets. They studied the influence of critical formulation and processing variables on scale-up of oral extended-release dosage forms, using hydrophilic polymer hydroxyl propyl methyl cellulose (Methocel K100LV). They concluded that change in polymer level was the most significant factor affecting drug release. Increase in Dicalcium phosphate level and compression force was found to affect the percent released at the later dissolution time points.

24. Raghavendra rao G, Gandhi Sagar, Patel Tarun., ***et al.***[67] work was to develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Zero order kinetics via, swelling, diffusion and erosion and the release profile of test formulation were comparable with the marketed product.

25. Sevgi Takka, Adel Sakr, Arthur Goldberg., ***et al.***[68] study was to develop an *in-vitro–in-vivo* correlation (IVIVC) for two Buspirone hydrochloride extended release formulations and to compare their plasma concentrations over time with the commercially available immediate release (IR) tablets developed two types of formulations using methocel high and low viscosity grades and evaluated that these will control the release.

26. K.Mahalingan, S.Rajarajan, N.Sree Harsha., (2009). ***et al.***[69] study to investigate the formulation development of orally administrable Clarithromycin delayed release tablet. **Clarithromycin** tablet was designed for the delaying the release to prolong the duration of drug action with the help of various polymers like Microcrystalline Cellulose, HPMC K4M, HPMC K5M, HPMC6CPS, PEG 6000 with different additives are used for the trial and error method .preliminary results from this study suggest that tablets prepared from MCC, HPMC 6CPS and PEG 6000 can be used to incorporate antibiotics like Clarithromycin and may be effective when administered orally in the stomach against H. pylori.

27. Brijesh S. Dave, Avani F. Amin, and Madhabhai M. Patel.., ***et al.***[70] purpose of this research was to prepare a gastroretentive drug delivery system of Ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxyl propyl methyl cellulose were evaluated for gel-forming properties. By selecting a suitable composition of release rate enhancer (citric acid) and release rate retardant (stearic acid), the desired dissolution profile can be achieved.

28. M. Harris shoaib, Jaweria Tazeen, Hamid Merchant and Rabia Ismail Yousuf ., *et al*.[71] Develop a once-daily sustained release matrix tablet of ibuprofen using hydroxyl propyl methyl cellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel PH 101 and Magnesium stearate. Ibuprofen sustained release matrix tablet was prepared successfully using HPMC as polymer to retard release and achieve required dissolution profile. Drug release kinetics of this formulation correspond best to Higuchi's model and drug release mechanism as per n value of Korsmeyer &Peppas (Power law) cannot be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion.

3: AIM AND OBJECTIVE

3.1. AIM:

The aim of the present study is to develop a pharmaceutically stable, cost effective and quality improved, once in a day formulation of Isradipine controlled release Matrix tablets by using synthetic polymer HPMC of different grades.

3.2. OBJECTIVE:

The concept of controlled drug delivery has been explored for the delivery of soluble and insoluble drugs for prolong period of time for the past few years. This type of drug delivery seems to provide a solution to several problems encountered in the course of design of the dosage form for such molecules. Utilizing the concept of incorporating drug in to the polymer matrices and extend the drug release for prolong period of time an attempt was made to design and evaluate a matrix tablets for a insoluble drug facilitating drug release by diffusion of the matrix using materials like polymers, waxes like hydrophilic and hydrophobic polymers to obtain the controlled release of the drug in vitro.

Isradipine belongs to dihydropyridine derivative, which is used as an anti-hypertensive agent and also as vasodilator since it is a calcium antagonist compound (calcium channel blockers). Isradipine is practically insoluble in water and its dissolution is rate limited by its physiochemical properties. Isradipine has a half life 1.5 to 8 hours and usual oral dosage regimen 2.5 mg to 20 mg. Also it undergoes extensive first-pass metabolism, resulting in a low bioavailability of 15%-24%. Hence to reduce the frequency of administration and to improve patient compliance, a once-daily controlled release formulation of Isradipine is desirable. Hydrophilic polymer matrix system were widely used in oral controlled drug delivery ,because they make it easier to achieve a desirable drug-release profile, they are cost effective and have US-FDA (Food Drug Administration) acceptance.

To achieve this goal various prototype formulation trials were taken and evaluated with respect to the various quality control tests such as dissolution, assay. The formula was finalized by comparing the *in vitro* dissolution profile.

Hence in present work, an attempt has been made to formulate Controlled release matrix tablet of Isradipine by using hydrophilic matrix material.

4: PLAN OF WORK

The present work was carried out to formulate and evaluate the controlled release matrix tablets of Isradipine using polymers like HPMC (E4M and E50). The study was proposed to carry out in the following stages.

Phase-I:

1. Pre-formulation study of pure drug.

2. Compatibility study.

   - Fourier transform infrared spectroscopy (FT-IR)

3. Preparation of standard curve of Isradipine.

Phase-II:

1. Formulation of Isradipine controlled release matrix tablets.

2. Evaluation of matrix tablets.

   - Physical evaluation.
   - Drug content.
   - Dissolution study.

3. Kinetic study.

Phase-III:

1. Accelerated stability study of the optimized formulation.

5. PROFILES

5.1. DRUG PROFILE

Isradipine:

Isradipine is a long-acting antihypertensive agent in vivo, exerting Primary effects on vascular tissue with secondary negative chronotropic action. Potent and selective L-type voltage-gated Ca2+ channel blocker. It belongs to dihydro pyridine class.

Structure:

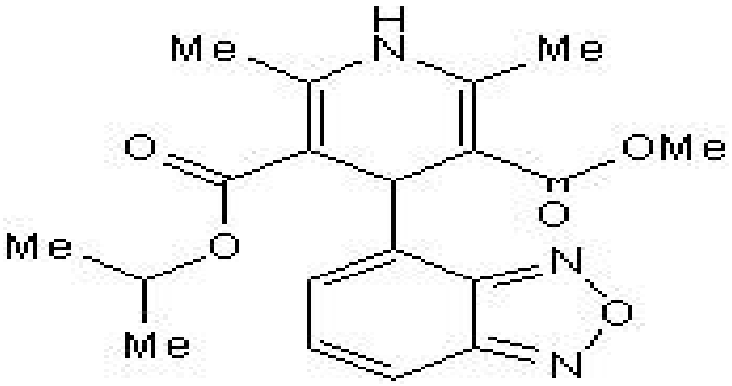


Table no: 3. Physico – Chemical Properties

Description	Yellow crystalline solid
Chemical name	4-(2,1,3-Benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinecarboxylic acid methyl 1-methylethyl ester
Molecular formula	$C_{19}H_{21}N_3O_5$
Molecular weight	371.39
Solubility	Isradipine is practically insoluble in water (<10mg/L at 37°C), but is soluble in ethanol and freely soluble in acetone, chloroform and methylene chloride.

Functional category	In the treatment of Hypertension, vasodilation.
Pharmacopoeial status	USP
Storage conditions	Store in air tight containers, Protect from light.

Site and Mode of Action:

Possibly by deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Isradipine inhibits the influx of extracellular calcium across both the myocardial and vascular smooth muscle cell membranes. The resultant inhibition of the contractile processes of the myocardial smooth muscle cells leads to dilation of the coronary and systemic arteries and improved oxygen delivery to the myocardial tissue.

Pharmacokinetics:

Absorption and distribution;

Isradipine is 90%-95% absorbed and is subject to extensive first-pass metabolism; resulting in a bioavailability of about 15%-24%.administration of Isradipine with food significantly increases the time to peak by about an hour, but has no effect on total bioavailability of the drug. Isradipine is 95% bound to plasma protein.

Metabolism and excretion;

Isradipine undergoes extensive first-pass metabolism; Peak plasma concentrations occur about2 hours after oral dosage Isradipine is extensively metabolized in the liver, at least partly by the cytochrome P450isoenzyme CYP3A4. About 70% of an oral dose is reported to be excreted as metabolites in urine, the remainder in faeces. The terminal elimination half-life is often stated to be about 8 hours although a value of less than 4 hours has also been reported. In single-dose and steady-state studies of the pharmacokinetics of Isradipine in 9 hypertensive subjects using a specific high performance liquid chromatographic assay, Isradipine was found to be rapidly absorbed with peak concentrations occurring 1.2(steady state) to 1.5 (single dose) hours after dosing.

The mean terminal elimination half-life at steady state was 3.8 hours, suggesting that duration of action is likely to be short and that Isradipine would need to be given at least twice daily. There was considerable inter individual variation in the pharmacokinetics. In an earlier study in healthy subjects the effective half-life of Isradipine was calculated to be 8.8 hours, but radiolabelled Isradipine was used and the assay method might have been less specific for unchanged drug.

Table no: 4. Pharmacokinetics-Pharmacodynamics

Parameters	Data
T_{max}	1.5 hr
Bioavailability	15-24%.
C_{max}	1ng/ml/mg
Volume of distribution(V_D)	3L/Kg
Clearance (CL_T)	1.4L/min
Biological half life	Biphasic with initial half of 1½-2hr,terminal half life of 8hr.
Site and Mechanism of absorption	Oral absorption
Serum protein binding	Highly serum protein bound (95%)
Route of metabolism	Rapidly metabolized in liver
Metabolites	Six metabolites have been characterized in blood and urine with the mono acids of pyridine derivative and a cyclic lactone product accounting for **>75**% of the material identified.
Activity of metabolites	Have very little or no activity

Route of excretion	Approximately 60-65% is excreted in urine and 25-30%in faeces.
Route of administration	Oral
Indications	Hypertension.
Adverse effects	Symptoms of overdose include lethargy, sinus tachycardia, and transient hypotension.

Drug Interactions with Isradipine:

Using this medicine with any of the following medicines is not recommended.

Bepridil, Cisapride, Levomethadyl, Mefloquine, Mesoridazine, Pimozide, Thioridazine, Ziprasidone

Using this medicine with any of the following medicines is usually not recommended, but may be required in some cases. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

Amiodarone, vasopressin, trimethoprim, satolol, risperidone, sulfamethoxazole, fluoxetine, amitriptylline.

Using this medicine with any of the following medicines may cause an increased risk of certain side effects.

Amprenavir, Dalfopristin, Indinavir, Itraconazole.

Dosage:

Hypertension: Adults: the usual initial dose is 2.5mg twice daily; Maximum dose 10 mg twice daily and doses increase to 20 mg daily if necessary.

5.2. EXCIPIENT PROFILE

Table no: 5. Hypromellose

Synonyms	Benecel, HPMC, Methocel, Hydroxy propyl methyl cellulose
Description	White or creamy white fibrous or granular, odorless, tasteless powder.
Functional categories	Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, viscosity builder.
Solubility	Soluble in cold water, forming a viscous colloidal solution, practically insoluble in mixtures of ethanol and dichloromethane, mixtures of alcohol and water.
pH	5.5-8.0 for a 1%w/w aqueous solution.
Bulk density	0.341 g/cm^3
Tapped density	0.557 g/cm^3
Melting point	Browns at 190-200 ^oC Chars at 225-230 ^oC
Moisture content	Absorbs moisture from the atmosphere.
Stability and storage conditions	Stable between pH 3-11, should be stored in a well-closed container in a cool and dry place.
Incompatibility	Incompatible with some oxidizing agents.
Applications	High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80%w/w in tablets and capsules. Low viscosity grades are used in aqueous film coating.

Table no: 6. Dibasic calcium phosphate dehydrate

Synonyms	Calcii hydrogenophosphas dihydricus; calcium hydrogen orthophosphate dihydrate; calcium monohydrogen phosphate dihydrate; Di-Cafos; dicalcium orthophosphate; DI-TAB; E341; Emcompress; phosphoric acid calcium salt (1 : 1) dihydrate;
Empirical formula	$CaHPO_4\_2H_2O$
Molecular weight	172.09
Description	White, odorless, tasteless powder or crystalline solid. It occurs as monoclinic crystals.
Functional categories	Tablet and capsule diluent
Solubility	Practically insoluble in ethanol, ether, and water; Soluble in dilute acids.
Loss on drying	24.5–26.5%(as per US pharmacopeia)
Stability and storage conditions	Dibasic calcium phosphate dihydrate is a non hygroscopic, relatively stable material. However, under certain conditions the dihydrate can lose water of crystallization. This has implications for both, storage of the bulk material and coating and packaging of tablets containing dibasic calcium phosphate dihydrate. The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Dibasic calcium phosphate dihydrate should not be used to formulate Tetracycline antibiotics. Dibasic calcium phosphate dihydrate has been reported to be incompatible with Indomethacin, Aspirin, Aspartame, Ampicillin, Cephalexin, and Erythromycin.

Applications	It is widely used as an excipient and as a source of calcium and phosphorus in nutritional supplements. Two main particle-size grades of dibasic calcium phosphate dihydrate are used in the pharmaceutical industry. The milled material is typically used in wet-granulated, roller-compacted or slugged formulations. The 'unmilled' or coarse-grade material is typically used in direct-compression formulations. It is also used in toothpaste and dentifrice formulations for its abrasive properties.

Table no: 7. Magnesium stearate

Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt;
Description	Magnesium stearate is a very fine, light white, precipitated milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol
Stability and storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts
Applications	Magnesium stearate is widely used in cosmetics, foods, and Pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% And 5.0% w/w. It is also used in barrier creams.

Table no: 8. Colloidal Silicone Dioxide.

Synonyms	Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumedsilica;
Description	Colloidal silicon dioxide is a sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.
Functional categories	Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.
Solubility	Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 258C (pH 7).
pH	3.5-5.5 for a 4%w/w aqueous solution
Bulk density	0.029–0.042 g/cm3
Melting point	1600 ^{0}C
Stability and storage conditions	Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced.
Incompatibility	Incompatible with diethylstilbestrol preparations
Applications	Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. (5Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nano capsules and nano sphere suspensions.

Table no: 9. Polyethylene Glycol

Synonyms	Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogol; PEG; Pluriol E; polyoxy ethylene glycol.;
Description	Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.
Functional categories	Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.
Solubility	Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.
pH	4.5-5.5 for a 5%w/w.
Flash point	238 ^{0}C
Stability and storage conditions	The temperature must be kept to the minimum necessary to ensure fluidity; oxidation may occur if polyethylene glycols are exposed for long periods to temperatures exceeding 508C. However, storage under nitrogen reduces the possibility of oxidation. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminium, glass, or lined steel containers are preferred for the storage of liquid grades.
Incompatibility	All grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. Liquid and solid polyethylene glycol grades may be incompatible with some colouring agents.

Applications	Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems. (1) Useful as ointment bases. Can be used as suppository bases, (3) for which they have many advantages over fats.

Table no: 10. Isopropyl alcohol

Synonyms	Di methyl carbinol, isopropanol , 2-propanol.
Empirical formula	$C_3 H_8 O$
Molecular wt	60.1
Description	Clear , colorless, mobile, volatile, flammable liquid with characteristic, spirituous odor & slightly bitter taste
Functional category	Disinfectant, solvent
Solubility	Miscible with benzene, chloroform, ethanol. Soluble in acetone Insoluble in salt solutions.
Storage conditions	Store in a airtight container in a cool & dry place
Incompatibility	Incompatible with H_2O_2 & Nitric acid. Salting out from aqueous preparations by adding sodium salts
Applications	Tablets - Film forming agent & Granulating agent 70% v/v used as disinfectant Not recommended for oral use

6. MATERIALS AND METHODOLOGY

6.1. MATERIALS

Table no: 11. List of materials used in the formulation study

S.No.	Name of the ingredients	Name of the Supplier
1	Isradipine	GlaxoSmithKline Pharmaceuticals Ltd., Nashik
2.	Dicalcium phosphate dehydrate (Calipharm D)	S.D. Fine chemicals Pvt. Ltd., Mumbai
5.	Methocel E4M	Strides Arco Labs, Bangalore
6.	Methocel E50	Strides Arco Labs, Bangalore
7.	Poly ethylene glycol (PEG -400)	S.D. Fine chemicals Pvt. Ltd., Mumbai
8.	Isopropyl alcohol	S.D. Fine chemicals Pvt. Ltd., Mumbai
9.	Aerosil	S.D. Fine chemicals Pvt. Ltd., Mumbai
10.	Magnesium stearate	S.D. Fine chemicals Pvt. Ltd., Mumbai

Table no: 12. Lists of equipment and instruments used in the present study

s. no.	equipment	manufacturer	model no
1	Electronic Balance	Shimadzu	AUX220
2	Sieves	United Engineering Ltd.	ASL00
3	Tap density Tester	Electrolab	ETD-020
4	Electromagnetic Sieve Shaker	Electropharma	EMS- 8
5	Laboratory Stirrer	Remi	RQT-124A
6	Rapid dryer	Retsch	TG-200
7	pH Meter	Thermo	Orion 2 Star
8	Dissolution test apparatus	Electro lab USP XXII	TDT-08L
9	Stability chambers	Thermolab	Standard
10	Hardness tester	Pharmatest	PTB-311E
11	Friabilator	Electrolab	EF-1W
12	Tablet Compression machine-16Station	Cadmch Machinery co. Pvt.Ltd	CM D3-16
13	Peristalic pump	Electrolab	PP-50V
14	IR moisture balance	Sartorious	SARTORIUS

6.2. METHODOLOGY FOR DEVELOPMENT OF CONTROLLED RELEASE MATRIX TABLET:-

6.2.1. PREFORMULATION STUDIES:

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational and development of dosage forms.

Objective/purpose of preformulation study:-

Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to serve following purposes:

i) To generate information useful in developing the formulation.
ii) To Finalize specifications of active pharmaceutical ingredients (API)
iii) To Study the compatibility between active and inactive ingredient

Scope:-

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Class: - Preformulation study can divide in to Two Subclasses.

I.API characterization,

II.Compatibility study

I. Active pharmaceutical ingredient (API) characterization:-

1. Organoleptic Evaluation: These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of Active Pharmaceutical Ingredients were studied. a) Color b) Odor

II. Determination of melting point:-

The melting point of isradipine was determined by capillary method, using definite quantity of isradipine taken and replaced in apparatus and determined the melting point and matched with the standards.

III. Loss on drying:-

1.0g of sample of isradipine was accurately weighed and the powder was kept in a moisture balance apparatus for 3 min. At 105ºC and the moisture content was calculated.

IV. SOLUBILITY STUDIES

Isradipine is classified under class II according to BCS i.e.; highly permeable but low soluble. Solubility studies of Isradipine were conducted at all pH ranges from 1 to 7.4. The solubility of Active Pharmaceutical Ingredients was determined by dissolving the highest unit dose of the drug in 250 mL of buffer adjusted between pH 1.0 and 7.4. For this purpose 0.1N HCl, pH 4.6 buffer, pH 6.8 buffer and 0.1%, 0.2% Lauryl Dimethylamine Oxide in water, Purified water were used. Highest dose of the drug i.e., 10mg was dissolved in 250 mL of medium and was kept untouched for 12 hours. Later on the insoluble drug was filtered off and diluted with sufficient amount of the same solvent. The absorbance of the solution was determined 239 nm.

V. Powder Characterization

1. Angle of Repose: -

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h / r$$

$$\theta = \text{Tan}^{-1} h / r \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad Eq\ (3)$$

Where

θ = angle of repose,

h = height,

r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed. The angle of repose was determined by measuring the height of the cone of powder and radius of the heap of powder.

Table no.13: Flow Properties and Corresponding Angles of Repose

Flow Property	**Angle of Repose (degrees)**
Excellent	25–30
Good	31–35
Fair - aid not needed	36–40
Passable - may hang up	41–45
Poor - must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Bulk density:-

Bulk density was determined by pouring gently 20 gm of sample (Isradipine) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram /volume occupied by the sample

3. Tapped density:-

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

Tapped density = Weight of sample in gram / Tapped volume

4. Compressibility Index and Hausner ratio:-

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

C.I = tapped-untapped×100/tapped.

$$\text{Carr's index} = \frac{\text{Tappeddesnity} - \text{Bulkdensity}}{\text{Tappeddensity}} \times 100$$

Table no.14: Relation of flow property with Compressibility index and Hausner's ratio.

Compressibility Index (%)	Flow Character	Hauser's Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

VI.DRUG EXCIPIENT COMPATIBILITY STUDIES

Drug Excipient Compatability Study by FTIR (Fourier Transform Infra-Red Spectroscopy)

Drug and excipient were analysed by IR spectral studies by using KBr pellet technique. IR spectrophotometry can be used to investigate and predict any physic-chemical interactions between different components in a formulation and therefore it can be applied to the selection of suitable chemical excipients.

The main aim of the study was to test whether there is any interaction between the mixtures of polymers and active pharmaceutical ingredient (Isradipine).

In this method, the drug and KBr were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FTIR spectra were recorded using KBr pellet method. Spectra were recorded for pure drug, pure excipients and drug with excipients.

VII. PREPARATION OF STANDARD CALIBRATION CURVE OF ISRADIPINE

Preparation of media (0.2% of 30% Lauryl Dimethyl amine oxide):

Transferred 66.0 mL of 30 % Lauryl Dimethyl amine oxide in to a 10 Litre of dearerated water and mixed well.

Method:

10mg of isradipine was accurately weighed and transferred into 100 ml volumetric flask, it was dissolved and diluted to volume with 0.2% Lauryl dimethyl amine oxide in water to give stock solution containing 1000µg/ml. the standard stock solution was then serially diluted with 0.2% Lauryl dimethyl amine oxide in water to give concentration of 1, 2, 3 upto 10µg/ml of isradipine. The absorbance was measured at 239 nm using UV Spectrophotometer, the absorbance values were plotted against concentration (µg/ml).

6.2.2. FORMULATION OF ISRADIPINE CONTROLLED RELEASE MATRIX TABLET

Based on preformulation data, wet granulation is used for developing matrix type dosage form. The following formulations are prepared by maintaining the effective processing conditions, NMT 50% RH and NMT 60 ºC temperature.

Formulation was done basically with strategies mentioned below

PROCEDURE FOR WET GRANULATION:

STEP 1. WEIGHING:

Weighed the required quantities of Isradipine, diluents (Dibasic Calcium Phosphate) and other dry mix elements as per given in the table separately.

STEP 2. SIFTING:

Co sifted the drug, diluent and HPMC E50 through #30 mesh and mixed the blend in a poly bag for uniform distribution of Active Pharmaceutical Ingredients.

STEP 3. LOADING AND GRANULATION:

Co sifted mixture is loaded into granulation apparatus and weighed required amount of water for granulation.

STEP 4. DRYING:

Granules were dried at temperature at 35-59 °C until the Loss on Drying was obtained.

STEP 5. SIZING OF GRANULES:

The granules obtained were sized through #30 mesh. Required quantity extra granular material was weighed and passed through #30 mesh along with granules.

STEP 6. LUBRICATION:

Required concentration of magnesium stearate was weighed, passed through #40 mesh and blended with blend from step 5 for 1 minute.

STEP 7. COMPRESSION:

The granules obtained were compressed with 8mm standard concave punch using 16 station compression machines.

Figure no.8: Formulation strategy of Isradipine 10 mg tablets.

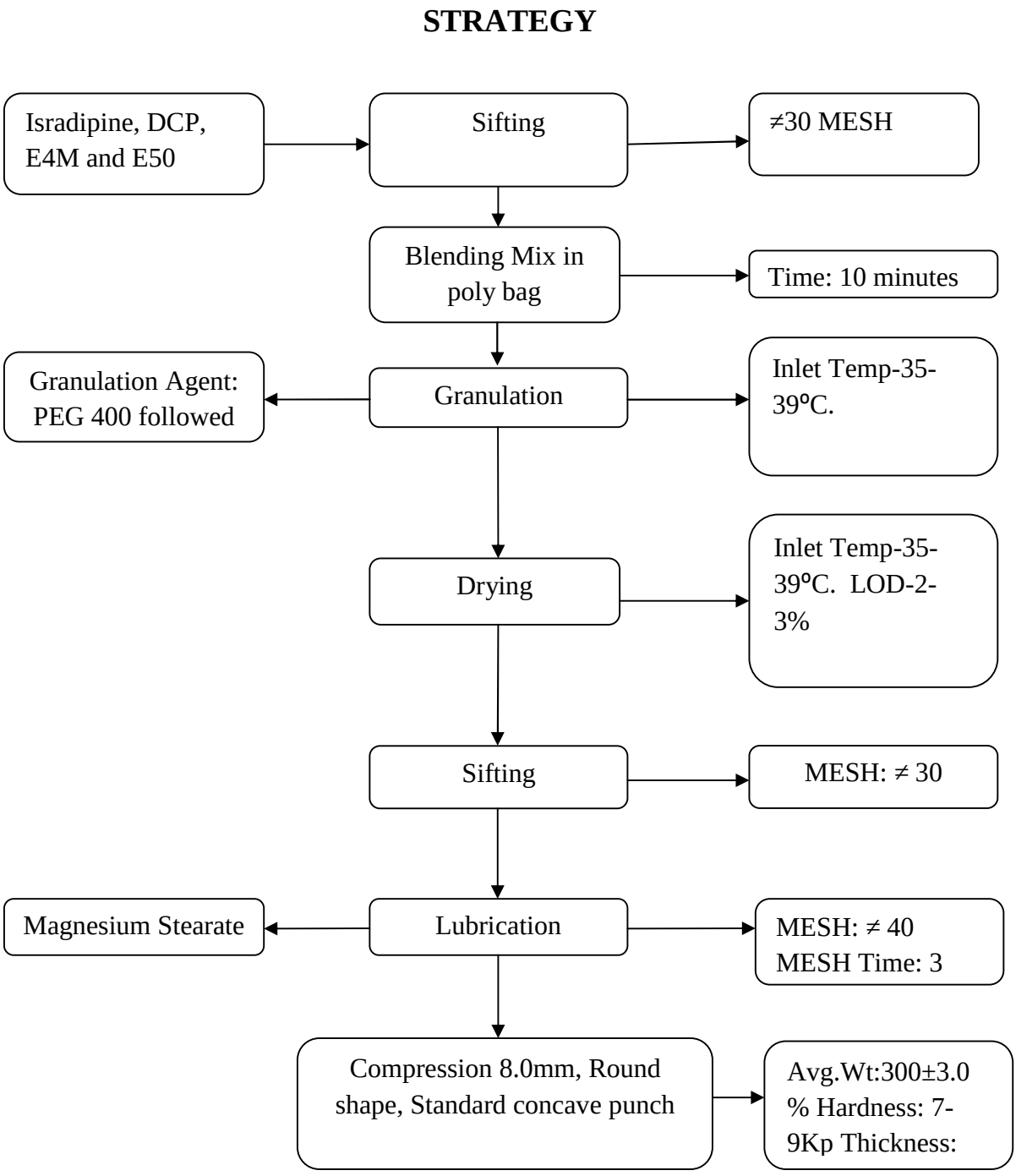


Table no.15: Tablets Compilation of Isradipine controlled release matrix tablet

S. NO.	CONTENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
					(mg/tablet)					
A. DRY MIX										
1	**Isradipine**	10	10	10	10	10	10	10	10	10
2	**Dibasic calcium phosphate**	210	210	210	210	210	200	210	200	200
3	**HPMC E4M**	50	60	70	-	-	-	60	60	60
4	**HPMC E50**	-	-	-	50	60	70	15	20	30
B. BINDER										
5	**PEG-400**	5	5	5	5	5	5	5	5	5
6	**Isopropyl alcohol**	1	1	1	1	1	1	1	1	1
C. LUBRICATION										
7	**Aerosil**	1	1.5	1.5	1.5	1	1	1.5	1	1
8	**Magnesium. Stearate**	2	2	2	2	2	2	2	2	2
Average weight		279	289	299	279	289	289	304	299	309

F=Formulation Batches

In F1: in the first trial F1,10 mg of isradipine,210 mg of DCP,50 mg of HPMC E4M were co sifted and PEG 400 was used as binder and granulated , lubricated with magnesium stearate and compressed.

In F2: same formula as that of F1, granulation is taken to that 60 mg of HPMC E4M was added, lubricated and compressed.

In F3: same formula as that of F1, granulation is taken to that 70 mg of HPMC E4M was added, lubricated and compressed.

In F4: same as that of F1, but here HPMC E4M was replaced for HPMC E50. Isradipine, DCP and HPMC E50 were co sifted and PEG 400 was used as binder and granulated, lubricated with magnesium stearate and compressed.

In F5: in formulation F5, in dry mix quantity of HPMC E50 first trial was increased to 60mg and isradipine DCP, HPMC E50 were co sifted and PEG 400 was used as binder and granulated , lubricated with magnesium stearate and compressed.

In F6: in formulation F6, in dry mix HPMC E50 was increased to70mg, and DCP decreased to 200 mg, then it was granulated, lubricated with magnesium stearate and compressed.

In F7: in formulation F7, both polymers were used in different ratio, 60 mg of HPMC E4M and 15 mg of HPMC E4M were added and co sifted PEG 400 was used as binder and granulated, lubricated with magnesium stearate and compressed.

In F8: same as in F7, here quantity HPMC E50 was increased to 20 mg, granulated, lubricated with magnesium stearate and compressed.

In F9: in formulation F9, HPMC E50 was increased to 30 mg and HPMC E4M was 60 mg was added, co sifted and PEG 400 was used as binder and granulated, lubricated with magnesium stearate and compressed.

6.2.3. PHYSICHOCHEMICAL EVALUATION OF TABLET

Post compression parameters:

a) Shape of tablet:

The compressed tablets were examined under the magnifying lens for the shape of tablet.

b) Tablet dimensions:

Diameters of the tablets were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

c) Hardness test:

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

d) Thickness:

Thickness of the tablet was calculated by the use of vernier calipers. The thickness of the tablet is measured in mm.

e) Friability test:

20 previously weighed tablets were placed in the apparatus. Which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = initial weight-final weight /initial weight × 100.

f) Weight Variation:

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

g) Drug content:

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of isradipine was transferred in to a 100 ml volumetric flask and volume made up with 0.2% lauryl dimethylamine in water. The mixture was then filtered to remove un-dissolved particle, further 1ml of the above solution was diluted to 10 ml with 0.2% lauryl dimethylamine in water and absorbance of the resulting solution was observed at 239 nm.

IN-VITRO DISSOLUTION STUDY:

Dissolution parameters:

Medium	: 0.2% Lauryl Dimethylamine Oxide (LDAO) in water
Apparatus	: USP- Type II (Paddle)
Rpm	: 50
Temperature	: $37^0 \pm 0.5^0$C
Medium volume	: 1000ml

Procedure:

1000 ml of 0.2% Lauryl Dimethylamine Oxide (LDAO) in water was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C $\pm$ 0.5°C. Tablet was placed in the vessel and

the vessel was covered the apparatus was operated for 24 hours and then the medium 0.2% Lauryl Dimethylamine Oxide (LDAO) in water was taken and process was continued from 0 to 24 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 239 nm using UV-spectrophotometer.

6.3. KINETICS OF DRUG RELEASE:

To analyze the mechanism of release and release rate kinetics of the dosage form , the data drug obtained were fitted into Zero order, First order, Higuchi matrix and korsmeyer-Peppa's and the correlation (r) values were calculated for linear curves by regression analysis of the above plot. Based on the r-value, the best –fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t \quad \text{.....} Eq\ (4)$$

Where,

Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution,

K_o = zero order release rate constant.

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a controlled release product.

First order kinetics:

To study the first order release rate kinetics, the release rate data were fitted to the following

equation,

Log Qt= log Qo+ K1t/2.303……..*Eq* (5)

Where,

Qt= the amount of drug released in time t,

Qo= the initial amount of drug in the solution

K1= the first order release constant.

In this way a graphic of the decimal log of the released amount of drug vs. time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in the porous matrices would release the drug in a way that is proportional to the amount of drug remaining in its interior.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

Qt= KH ·t1/2……..*Eq* (6)

Where,

Qt= amount of drug released in time t,

KH = Higuchi dissolution constant.

It describes drug release as a function of square root of time that is dependent on diffusion process based on Fick's law.

Krosmeyer and Peppas release model:

For prediction of mechanism of drug release through polymeric system Korsmeyer and Peppas, in 1983 developed a mathematical equation, relating exponentially the drug released to the elapsed time. It is a simple semi empirical equation also called as Power law.

To study this model the release rate data are fitted to the following equation,

$$Mt / M\infty = K \cdot t^{n} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \textit{Eq}\ (7)$$

Where,

Mt / M∞ = the absolute cumulative of drug release at time t and infinite time.

K = the release constant,

T = the release time,

N = the diffusion coefficient for the drug release that is dependent on the shape of the matrix dosage form.

Table No.16: Release Kinetics

DIFFUSION EXPONENT Release Exponent(n)	**OVERALL SOLUTE DIFFUSION MECHANISM Drug Transport Mechanism**
0.45 0.5	Fickian Diffusion SLAB/CYLINDER
0.45<n<0.89 0.5<n<1.0	Anomalous (Non Fickian)Transport SLAB/CYLINDER
0.89 1.0	Case II SLAB/CYLINDER
n>0.89 n>1.0	Super Case II Transport SLAB/CYLINDER

From the Table 16, it is clear that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero order release kinetics. For slabs, the mechanism that creates the zero-order release is known to polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring upon water imbibitions into the system is the rate controlling step. The value of n= 0.5 indicates drug release is Fickian in nature. Thus, Equation has two distinct physical meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1 (indicating swelling-controlled drug release). Values of *n* between 0.5 and 1.0 can be regarded as an indicator for the superposition of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent *n*, 0.5 and 1.0, are only valid for slab geometry. Power Law is more comprehensive in describing the drug release as compared to Higuchi.

6.4. STABILITY STUDY

An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. This can be ensured only by instituting a sound programmed to study the stability of a product during its various phases of development and to arrive at the proper storage conditions and the expiry period under those conditions. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries. These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and save invaluable time and effort from being spend on an unmarketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing worldwide under various climatic conditions including tropical, subtropical and temperate.

Storage conditions

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The storage condition used for stability studies were accelerated condition ($40^0C \pm 2^0C$/75% ± 5% RH) as per ICH guidelines. Stability study was carried out for for the optimized formulation. Tablet of optimized formulation were striped packed and kept in stability chamber for 3 month on above mention temperature.

7. RESULTS AND DISCUSSION

7.1. Preformulation Studies

I. Organoleptic evaluation

Yellow colored fine crystalline powder odorless.

II. Melting point determination

Melting point of Isradipine was given in table no.17; it indicates purity of the drug sample

Table no.17: Melting point observation

Test	Specification	Observation
Melting point	168-170^{0}C	169^{0}C

III. Loss on drying

It was determined as per procedure given in methodology. The results are illustrated in following table

Table no.18: Observation for Loss on drying

Test	Specification	Observation
Loss on drying	Not more than 0.5%	0.27%

IV. Solubility study

The solubility studies of Isradipine in water / buffer solutions were carried out to know the solubility and decide the appropriate dissolution medium. Table 6 shows the solubility data of of Isradipine in water/ buffer solutions.

Table no.19: Solubility study data of Isradipine

Test	Name of the buffer/solvent	Observation
Solubility Analysis	Water	0.091mg/ml
	0.1NHCl	0.037mg/ml
	P^H 4.5 Acetate buffer	0.05mg/ml
	P^H 6.8 Phosphate buffer	0.06mg/ml
	0.1%LDAO	0.427mg/ml
	0.2%LDAO	0.654mg/ml

V. Powder characterization

The results are illustrated are the table given below. The given result is an average of three determinations.

Table no.20: Determination of Powder characteristic

S.no	Characteristics	Results
1.	Angle of repose	$49^0.56'$
2.	Bulk density	0.39 g/ml
3.	Tapped density	0.221 g/ml
4.	Compressibility index	41.11%
5.	Hausner's ratio	1.698

VI. DRUG EXCIPIENTS COMPATIBILITY STUDY

FTIR-STUDY:

The FT-IR spectrum of pure Isradipine was compared with the FT-IR spectrum of physical mixtures of isradipine (isradipine, HPMC E50, HPMC E4M).There was mo appearance or disappearance of any characterstics peaks. This shows that there is no chemical interaction between the drug and the polymers used in the tablets. The presence of peaks at the expected range confirms that the materials taken for the study are genuine.

Table no.21: FT-IR Peak of various components

Wave number in cm-^{1}	**Characteristic bands**	**drug**
900-670	C-H stretching	780 cm-^{1}
1720-1700	C=O	1710 cm-^{1}
1615-1510	CH-CH_2CH_2	1540 cm-^{1}
2850-2815	O-CH_3	2827 cm-^{1}
1680-1620	C=C	1670 cm-^{1}
1690-1590	C=N bending	1630 cm-^{1}

Figure no.9: FT-IR Spectrum of Isradipine

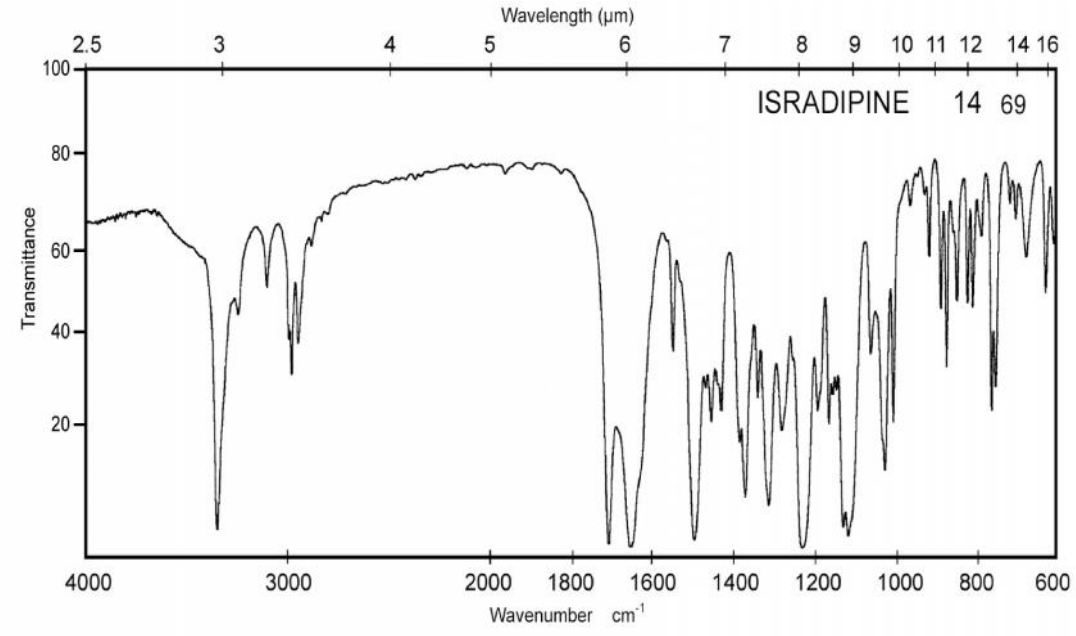


Figure no.10: FT-IR Spectrum of ISRADIPINE+HPMC E4M

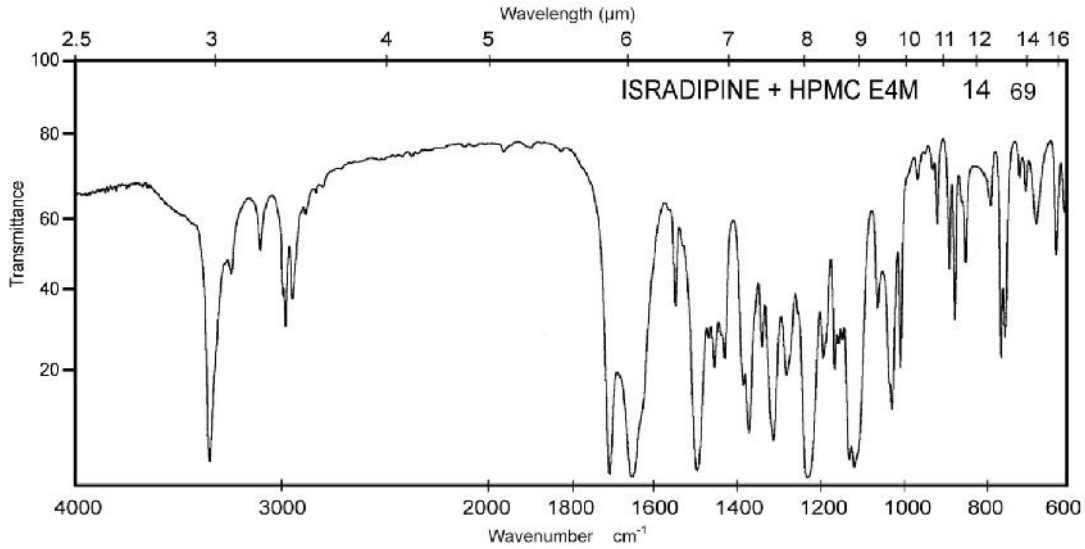
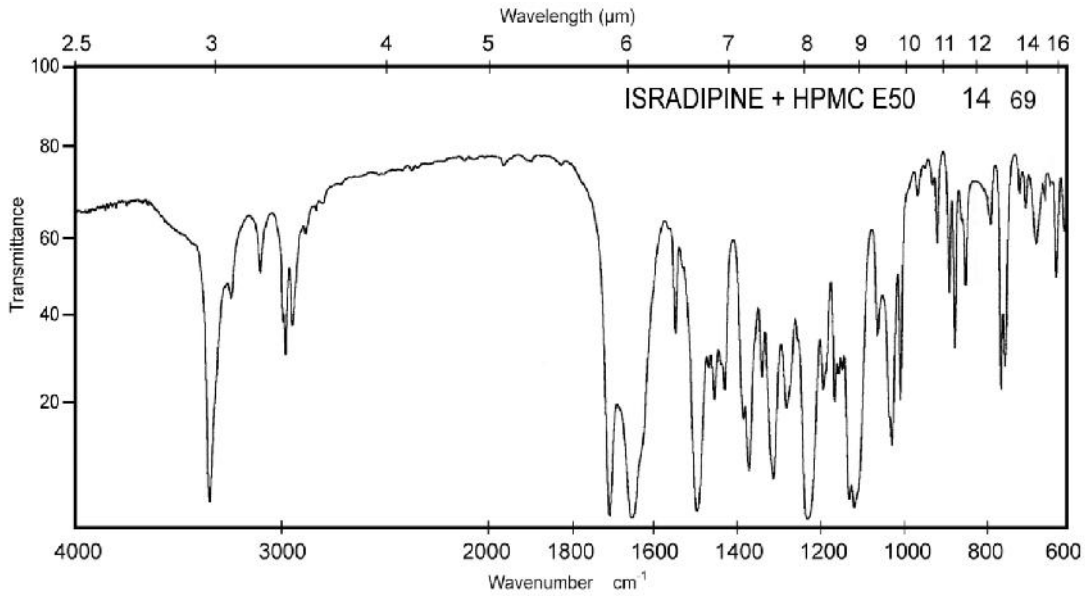


Figure no.11: FT-IR Spectrum of isradipine +HPMC E50



7.2. STANDARD CALIBRATION CURVE OF ISRADIPINE:

Standard curve of isradipine was determined by plotting absorbance(nm) versus concentration (µg/ml) at 239 nm and it was found to follow the beer's law in the range of 1to10µg/ml. the results obtained are as follows:-

Table no.22: standard curve of isradipine

Sl no.	Concentration(µg/ml)	Absorbance
1	0	0
2	1	0.0906
3	2	0.1563
4	3	0.223
5	4	0.2901
6	5	0.3618
7	6	0.4199
8	7	0.4879
9	8	0.5801
10	9	0.6407
11	10	0.7184
Slope		0.071
Regression		0.998

The linear regression analysis was done on absorbance data points.

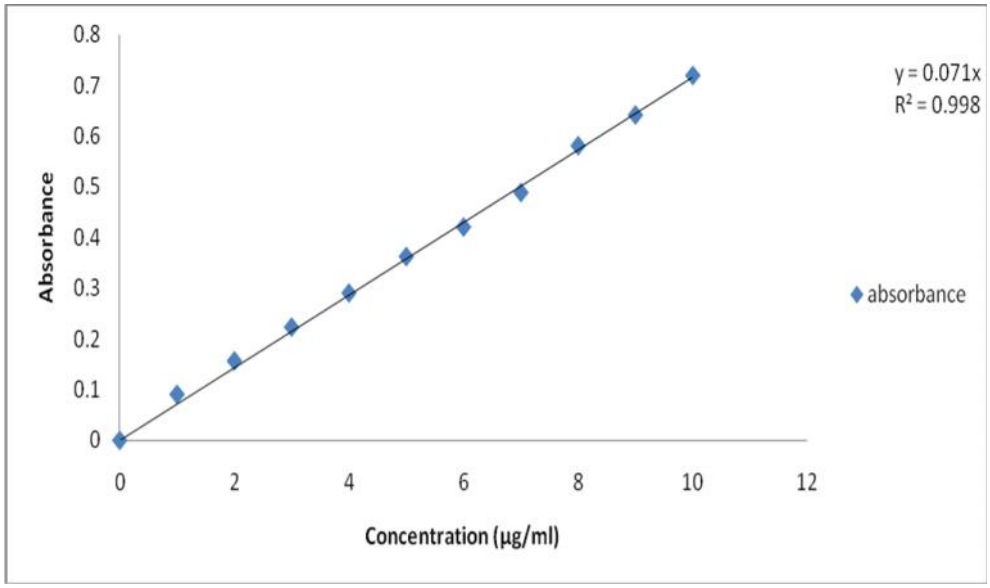
A straight line equation was generated to facilitate the calculation of amount of drug. The equation is as follows.

(y=mx+c)

Where,

Y=absorbance, m=slope, x = concentration, c = intercept.

Figure no.12: standard curve of isradipine



7.3. EVALUATION OF ISRADIPINE CONTROLLED RELEASE MATRIX TABLETS

a) Shape of tablet:

Visual examinations of tablets from F1 to F9 were found to be circular shape with no cracks.

b) Tablet dimensions:

The dimensions determine for formulated tablets were found to be uniform in formulation F1 to F9.

c) Hardness:

The hardness of all batches ranged from 5 to 10 kp which was sufficient to maintain the mechanical strength.

d) Thickness:

The thickness of the formulations was found in the range of 3-5mm. The tablets exhibited uniform thickness among the different formulations .It is depicted in table no.

e) Weight variation test:

All the formulated tablets passed weight variation test as pr the pharmacopoeia limits of ± 5%.

f) Friability:

The value of % friability of each batch was found to be in range of 0.37 to 0.91.

g) Drug content:

The percentage of drug content from F1 to F9 was found to be 98.91% to 99.94% of Isradipine. The average drug content of 10 tablets of each formulation is depicted in Table no. Good uniformity in drug content was found among different batches of the tablets and the percentage content was within ±10%.

Table no.23: Results of Physical Evaluation of tablet

Batch code	Physical Parameters					
	Diameter (mm)± S.D	**Hardness (Kg/Square inch)**	**Thickness (mm)**	**Weight variation**	**Friability (%)**	**Drug content (mg) ±S.D**
F1	13.09±0.040	6-7	3.8-4.2	1.44	0.72	99.22±0.08
F2	13.08±0.006	5-6	3.94	1.23	0.79	99.09±0.04
F3	13.09±0.067	6-.7	4.00	1.48	0.81	99.79±0.0
F4	13.08±0.070	7-8	2-2.5	1.63	0.86	99.83±0.05
F5	13.08±0.056	7-9	3.8-4.1	1.38	0.91	99.17±0.04
F6	13.08±0.056	7-9	4.8-5.0	1.24	0.75	99.52±0.08
F7	13.09±0.052	7-9	3-4	1.28	0.67	99.53±0.04
F8	13.10±0.040	7-9	3-4	1.20	0.61	99.35±0.02
F9	13.28±0.067	7-9	3.3-3.5	1.20	0.46	99.69±0.05

7.3.1. DISSOLUTION STUDIES:

The dissolution was carried out for different experimental trials and also for the innovator. The various results that are obtained are tabulated below. Dissolution studies are carried out in the following media.

Medium	: 0.2% LDAO in water
Type of apparatus	: USP - II (paddle type)
RPM	: 50 rpm
Volume	: 1000 mL
Temperature	: 37ºC± 0.5^0C
Time	: 24 hours

Dissolution profile for Isradipine controlled release matrix tablets:

Table no.24: Dissolution data for Isradipine formulation F1, F2 and F3

Time (hours)	Cumulative percentage drug release		
	F1	F2	F3
0	0	0	0
2	12.0	12.16	13.0
4	20.25	22.65	24.30
6	32.61	35.14	36.42
8	45.36	49.31	52.34
10	61.72	64.45	67.71
12	71.88	75.67	77.67
16	80.36	81.65	88.62
24	90.73	91.12	92.87

Figure no.13: Dissolution profile for Isradipine formulation F1, F2 and F3

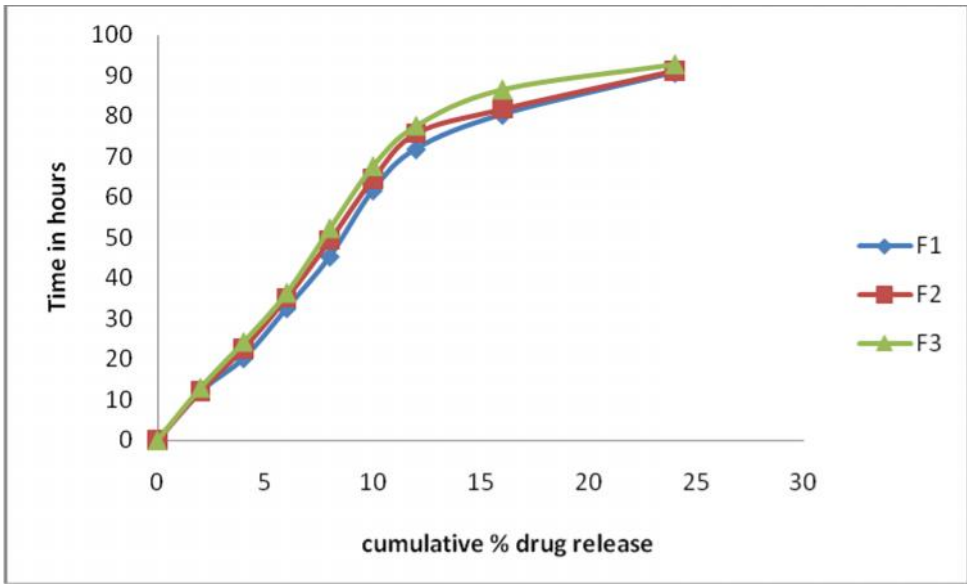


Table no.25: Dissolution data for Isradipine formulation F4, F5 and F6

Time (hours)	Cumulative percentage drug release		
	F4	**F5**	**F6**
0	0	0	0
2	24.29	24.7	22.17
4	37.43	36.42	33.72
6	52.13	52.0	51.14
8	65.82	64.79	61.32
10	76.55	75.41	72.63
12	88.38	82.62	84.27
16	98.68	97.0	93.05
24	–	–	–

Figure no.14: Dissolution profile for Isradipine formulation F4, F5 and F6

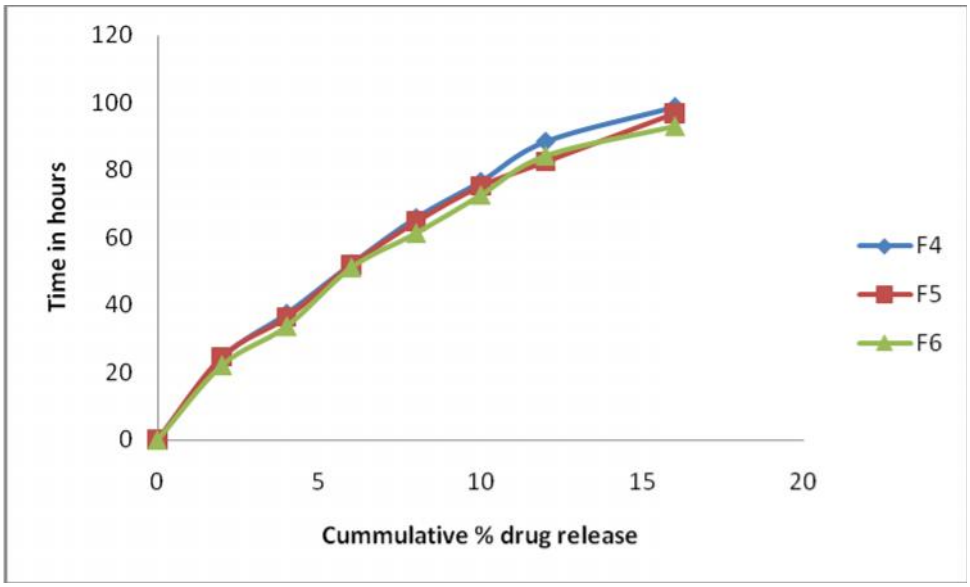


Table no.26: Dissolution data for Isradipine formulation F7, F8 and F9

Time (hours)	Cumulative percentage drug release		
	F7	F8	F9
0	0	0	0
2	13.01	15.01	17.00
4	23.0	25.26	30.16
6	36.30	39.84	43.80
8	55.0	57.06	60.04
10	68.40	69.29	74.39
12	82.01	84.17	89.00
16	89.08	91.10	94.11
24	94.15	96.30	99.08

Figure no.15: Dissolution profile for Isradipine formulation F7, F8 and F9

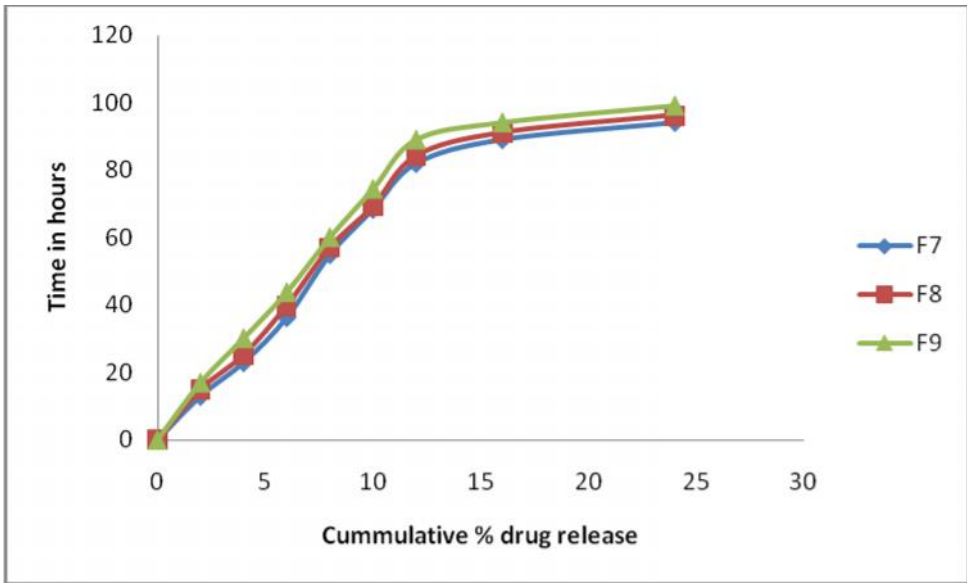
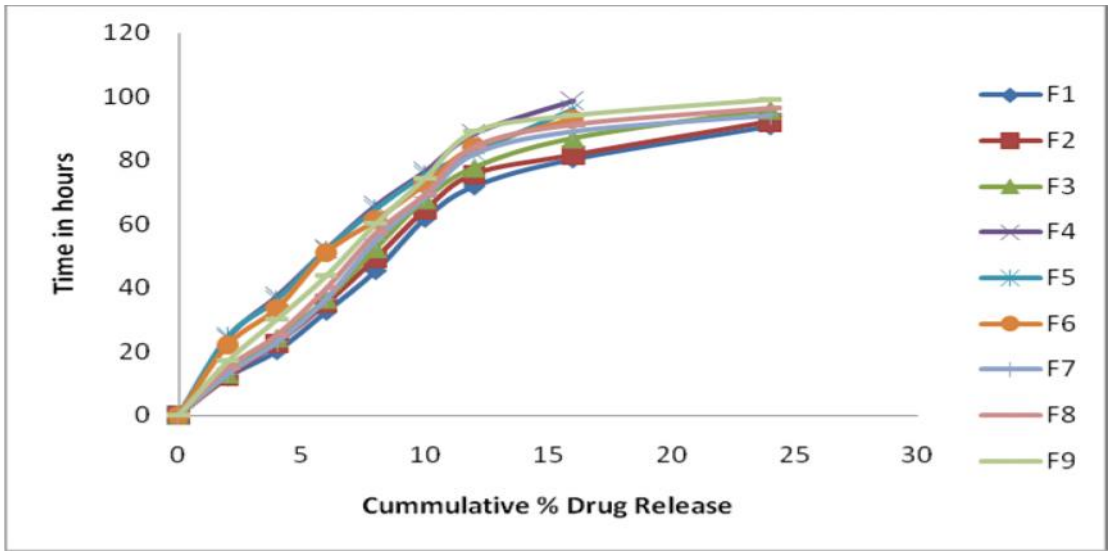


Table no.27: Comparative dissolution profile of F1 to F9

Time (hours)	Cumulative percentage drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
2	13.0	12.16	12.0	24.29	24.7	22.17	13.01	15.01	17.00
4	24.30	22.65	20.25	37.43	36.42	33.72	23.0	25.26	30.16
6	36.42	35.14	32.61	52.13	52.0	51.14	36.30	39.84	43.80
8	52.34	49.31	45.36	65.82	64.79	61.32	55.0	57.06	60.04
10	67.71	64.45	61.72	76.55	75.41	72.63	68.40	69.29	74.39
12	77.67	75.67	71.88	88.38	82.62	84.27	82.01	84.17	89.00
16	88.62	81.65	80.36	98.68	97..0	93.05	89.08	91.10	94.11
24	92.87	91.12	90.73	_	_	_	94.15	96.30	99.08

Figure no.16: Comparative Dissolution profile for Isradipine formulation F1 to F9



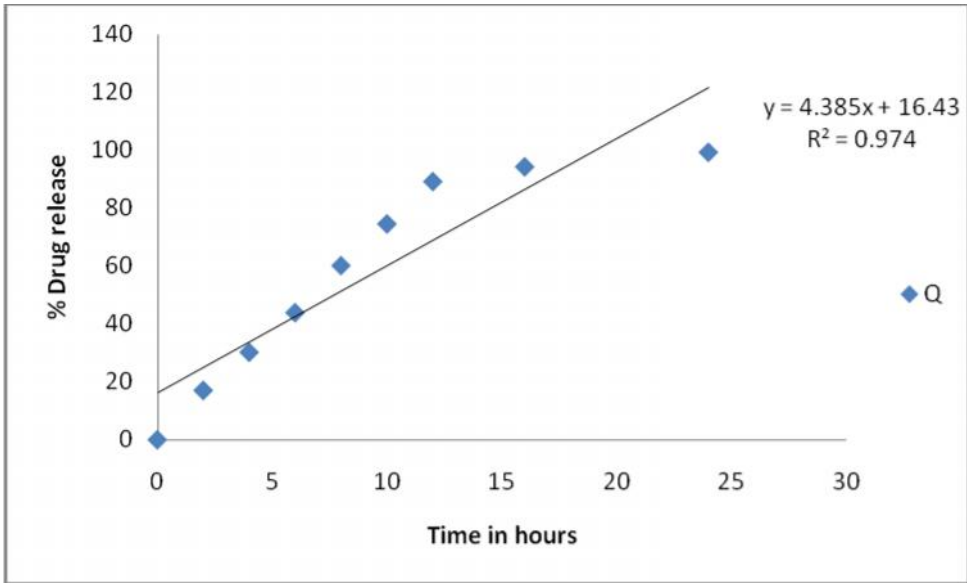
7.3. KINETIC STUDIES:

Table no.28: Kinetics of Isradipine controlled release matrix tablet F9

S.no	Time	Log time	Square root of time	% drug release (q)	% drug remaining (100-q)	Log(q)	Log (100-q)
				F9	F9	F9	F9
1	0	-	0	0	100	-	2
2	2	0.3	1.41	17.00	83	1.23	1.91
3	4	0.6	2	30.16	69.84	1.47	1.84
4	6	0.8	2.45	43.80	56.2	1.64	1.74
5	8	0.9	2.83	66.04	33.6	1.81	1.52
6	10	1	3.16	74.39	25.61	1.87	1.40
7	12	1.1	3.46	98.00	11	1.94	1.04
8	16	1.2	4	94.11	5.89	1.97	0.77
9	24	1.4	4.90	99.08	0.92	1.99	0.03

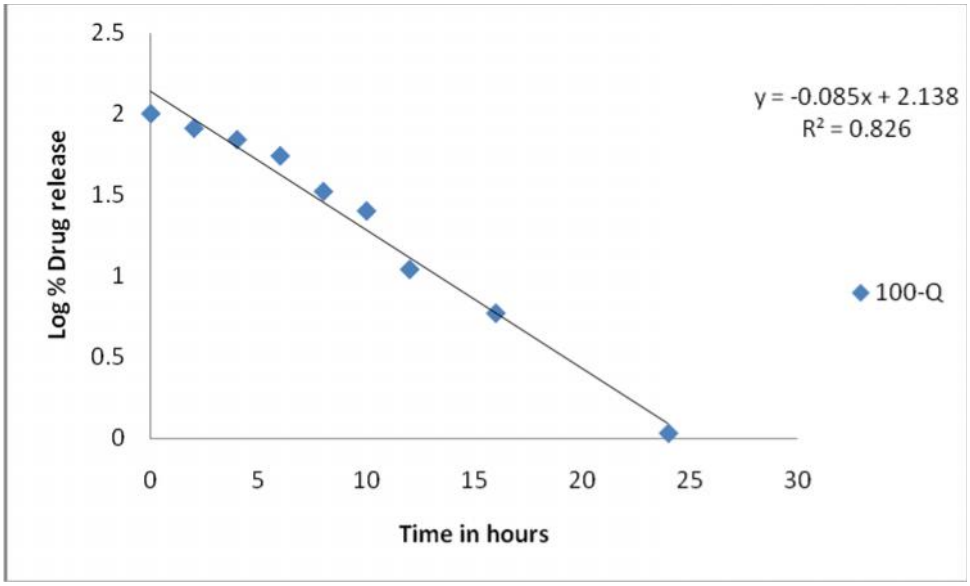
ZERO ORDER KINETICS: **S**

Figure no.17: Zero order plot of F9



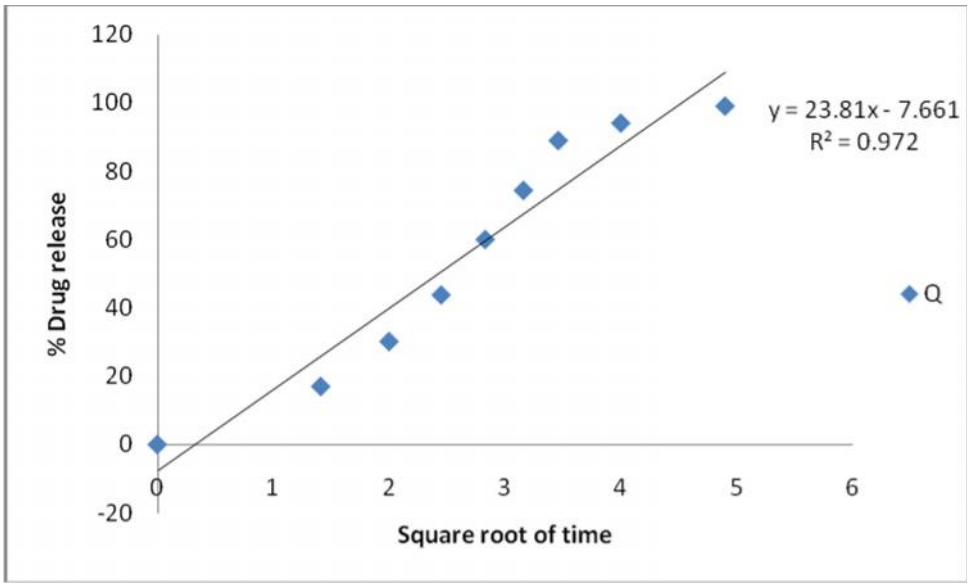
FIRST ORDER KINETICS:

Figure no.18: First order plot of F9



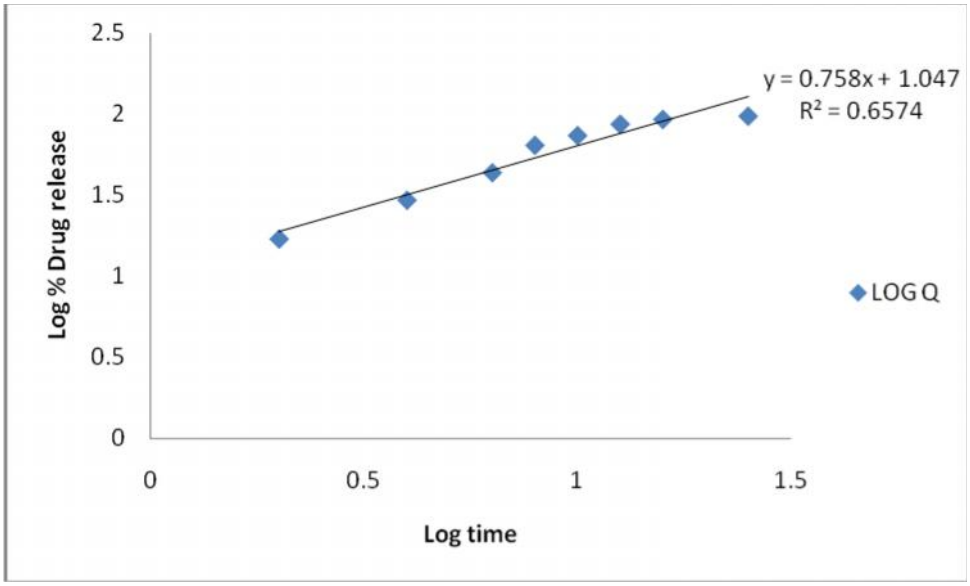
HIGUCHI PLOT:

Figure no.19: Higuchi plot of F9



KORESMEYER PEPPAS PLOT

Figure no.20: Koresmeyer-peppas plot of F9



KINETIC VALUES OBTAINED FROM PLOTS OF F9 FORMULATION OF ISRADIPINE

Table no.29: compilation of results from all the mathematical models applied to the optimized formulation.

Formulas	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-peppas R^2	n	Mechanism of drug release
F9	0.974	0.826	0.972	0.6574	0.758	Zero order non fickian diffusion

7.4. ACCELERATED STABILITY STUDIES

Isradipine controlled release matrix tablets were evaluated for accelerated stability studies at 40^0C / 75 % RH condition. The stability details / results are presented as below.

Storage Condition: 40^0C / 75 % RH

Pack: HDPE (High Density Polyethylene) Container

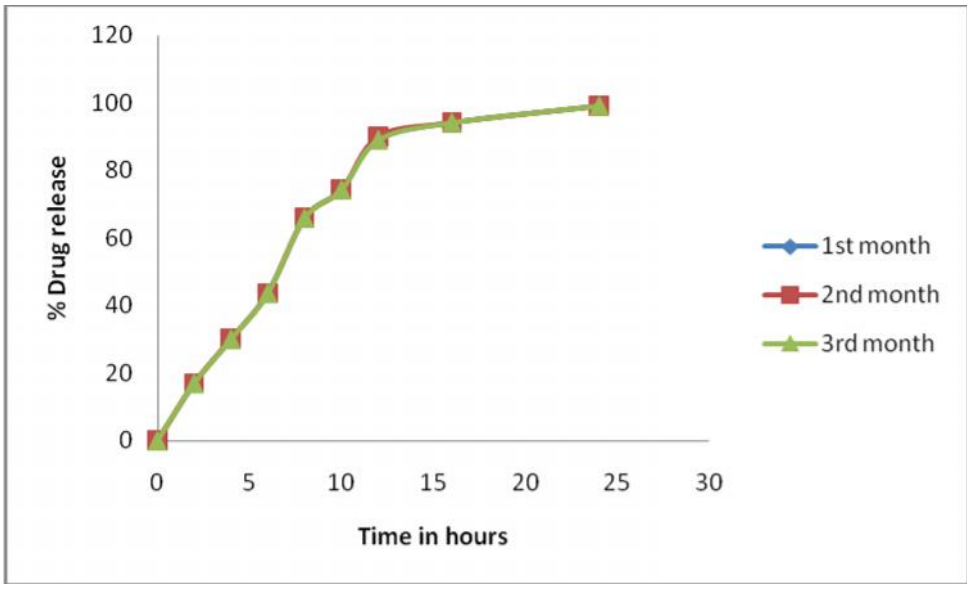
Storage Period: 1 month, 2 months and 3 month

Cumulative Dissolution profile of tablets after 1st month, 2nd month and 3rd month stability of F9:

Table no.30: comparative dissolution data

Time in hours	Cumulative % drug release		
	1st month	2nd month	3rd month
0	0	0	0
2	17	16.99	16.93
4	30.1	30.07	30.02
6	43.73	43.69	43.61
8	65.89	65.82	65.79
10	74.27	74.21	74.19
12	88.95	89.9	88.87
16	94.08	94.08	94
24	99.02	99.02	98.99

Figure no.21: Dissolution Profile After 1st month, 2nd month and 3rd month stability of F9



7.5. DISCUSSIONS

7.5.1. Preformulation studies of pure drug

Morphological characteristics such as colour, odour, form etc; of isradipine were studied. As the API is found to be yellow colour and odourless.

The Melting point of isradipine lies in the range between 168-170˚C, which indicates the purity of the drug and also indicating that drug has less sensitivity for drying temperatures.

The solubility of isradipine was analysed in various media at different pH. It was found that the drug was insoluble in water and soluble in Acetone, Ethanol Isopropyl alcohol and Dichloro methane. Based on solubility the dissolution media was selected and it is also official media 0.2% Lauryl Dimethyl Amine Oxide in water.

Flow properties of API were studied by performing tests like Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio. The results indicate that Angle of repose of pure drug is greater than 40 indicating poor flow properties. The Carr's index was found to be 27% indicating fair to passable. The Hausner's ratio was within the limits indicating free flowability. These results indicated the drug possessed good flow properties and compressible characteristics.

7.5.2. Drug excipient compatibility studies:

IR spectra of physical mixture of drug and excipients, drug alone showed no significant shift or reduction in intensity of peaks of isradipine. The studies showed that there was no interaction or physical change between the drug and excipients. So the selected excipients were found to be compatible with the drug.

7.5.3. Preparation of calibration curve

Estimation of isradipine was performed by UV spectrophotometric method. The method obeyed Beer's of drug and law in the concentration range of 0-10µg/ml. Thus the method was found to be suitable for estimation of isradipine content in various

products and in vitro dissolution studies. The result was showed that there was no shown in Fig 12.

7.5.4. Formulation studies of isradipine Controlled release matrix tablets:

Isradipine along with other excipients was formulated into tablets by wet granulation methods as per the formulae given in the table no.15. HPMC was used in graded amounts as to control the rate of release. Isopropyl alcohol and PEG in suitable ratios were used as granulating agents.

All the tablets prepared were found to contain the drug with in 99.46±4 % given in table no. 23. Hardness of the tablets was in the range of 5-9 kg and was satisfactory. The % weight loss in the friability test was less than 0.5 in all the tablets prepared.

Thus all the tablets were found to be of good quality and fulfilling all the official and other requirements of compressed tablets.

Among all the tablets formulated, formulation F9 prepared by wet granulation gave the highest dissolution(99.08%) in a controlled release manner.So formulation F9 was considered as best and optimized for the preparation of tablets of isradipine prepared by wet granulation.

The dissolution data and dissolution profiles of isradipine controlled release matrix tablets formulated were given in table no. 27 and shown in figure no 16.

7.5.5. Release mechanism

Based on the "n" value of 0.758 obtained for F9 formulation, the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

Also, the drug release mechanism was best explained by zero order equation as the plots showed the highest linearity (r^2 = 0.9743), followed by Higuchi's equation (r^2 = 0.9729). As the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release is concentration independent.

7.5.6. Accelerated stability study

Stability studies were carried out at 40°C and 75% RH for three month (Climate Zone IV condition for accelerated stability testing) to access their long term stability. The protocol of stability studies were in compliance with the guidelines in the WHO document for stability testing for product intended for the global market. After storage the formulation was subjected to physical evaluation and % drug release after storage condition of 40°C and 75%RH for three month shows not significant change. The stability studies result is shown in table no.30 and figure no.21.

8. SUMMARY AND CONCLUSION

8.1. Summary

The aim of this study was to develop the Isradipine Controlled Release Matrix tablets. Isradipine is long acting hypertensive agent, which is used in the treatment of hypertension. In this study Isradipine matrix tablets were prepared by using excipients like HPMC E50 and HPMC E4M, (were used as matrix formers) and formulated by wet granulation method, were subjected to physicochemical and in vitro dissolution studies .

The conclusion of the study is as follows:

- In the preformulation studies, it was found that Isradipine has low solubility with independent of P^H, i.e. it is soluble in 0.2% LDAO in water.
- The FT-IR spectroscopy study was carried out to know the compatibility of the excipients with Isradipine Results was found no significance changes in characteristic peaks of drug in the recorded IR spectrum. Which it confirmed the drug and other excipients used in the formulation are compatible with each other.
- The analytical method used in the present study was found to be suitable for the estimation of Isradipine in different Medias which is indicated by the high regression values obtained in the standard plots.
- The controlled release matrix tablets were prepared by wet granulation method using PEG-400 and Isopropyl alcohol as binder and dibasic calcium phosphate as diluents. Tablets prepared were found to be within the official limits with respect to hardness, weight variation, drug content, thickness etc.
- Among all the nine formulations the release profile of trial F9 was found to be able to control the rate of release for 24 hours.
- The best linearity was found in Higuchi's equation plot for formulation indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion.
- The dissolution data was also plotted in accordance with Korsmeyer-peppas model (where n is the release exponent). Applicability of data indicating Non

Fickian diffusion (or) Anomalous Transport as mechanism of drug release. Non Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient.

- The stability study for the selected formulation F9 was performed as per ICH guidelines. Stability study is carried out for three months at 40°C; 75% RH, according to ICH guidelines. The tablets were tested for release during the stability period and confirmed that results were found within the limits.
- The stability data reveals that the F9 showed a negligible change in drug content after storage in various conditions for three months according to ICH guidelines.

8.2. Conclusion

By observing the results it can be concluded that formulation-F9 containing Isradipine 10 mg per tablet and developed employing dibasic calcium phosphate and Hydroxy propyl methyl cellulose gives better controlled release profile compare with other formulation.

No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of three months at 40^{o} C and 75% RH. Hence the study resulted in the development of Isradipine Controlled Release Matrix tablets comparable to the innovator product for Isradipine fulfilling the objective of the study.

The identified formula shall be utilized for the formulation development and other studies for successful launching of the product as it was proved to be stable and robust, cost effective compared to osmotic device.

Hence the above study demonstrated that combination of various significant viscosities of hydrophilic polymers and wet granulation ratios could be successfully employed for formulating controlled release matrix tablet of isradipine. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional isradipine tablets.

Hence it can be concluded that once daily controlled release tablet of isradipine having satisfactory controlled release profile which may provide an increased therapeutic efficacy thereby improving bioavailability and patient compliance. The developed formulation overcomes and alleviates the drawback and limitation of controlled Isradipine Controlled release preparations thereby fulfilling the objective of the study.

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